



Sensitization following occupational exposure to methyl aminolevulinate: Report of two cases

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Photodynamic therapy (PDT) is widely used for treatment of different types of nonmelanoma skin cancers. After a gentle curettage, the photosensitizer, 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), is applied under occlusion for 3 hours. ALA or MAL penetrates the skin and is converted enzymatically into protoporphyrin IX. Through light activation, cytotoxic oxygen species are produced that lead to selective destruction of neoplastic cells. Besides the expected side effects, such as erythema, edema, and erosive lesions, patients with clinically relevant allergic contact dermatitis to the photosensitizers used have been described.^{1–6} In 2011 the first case of allergic contact dermatitis caused by occupational exposure to MAL was reported by Pastor-Nieto et al.⁷ We herein report on two more patients with occupational exposure to MAL.

CASE REPORT

Case 1

A 60-year-old woman presented with erythematous and hyperkeratotic lesions as well as painful fissures on both hands, especially at her fingertips. These have been persisting for several years and only improved during longer absence from her workplace. The patient had suffered from hand eczema before, around the age of 20, and has several known contact allergies, including those to dichromate, *Myroxylon pereirae*, nickel, and hydroxyisohexyl 3-cyclohexene carboxaldehyde. Her current daily work included application and removal of ALA, MAL, and occlusive dressings on several patients per day, with gloves worn on a regular basis. The patient has been working in the field of PDT for over 20 years (5 days a week) and has been exposed to MAL for more than 17 years.

Case 2

A 57-year-old woman working in the same department for about 10 years, 5 days a week, performing the same tasks as described for patient 1. She has never suffered from hand eczema or other skin diseases and has a known allergy to gold sodium thiosulfate. During history taking she reported slight rhinitis symptoms when removing the occlusive dressing and photosensitizer from patients.

Both patients were tested to all photosensitizers (Mevix, Ameluz and liposomal ALA gel 3%), each at a dilution of 50%. In addition, they were tested separately to methyl 5-aminolevulinate hydrochloride 21% in petrolatum and the 13 excipients of Mevix kindly provided by the manufacturer (Galderma Laboratorium, Düsseldorf, Germany). Patches were removed after 1 day, readings performed on day (D) 1, D2, and D3. Both patients showed positive reactions to Mevix and methyl 5-aminolevulinate hydrochloride on D1, D2, and D3 (Figure 1). Patient 1 had a follicular reaction to Ameluz on D2 and D3. Testing for allergy to liposomal ALA gel 3% as well as the Mevix excipients was negative in both patients (Table S1). In addition, both patients received prick-to-prick testing with Mevix, Ameluz, and liposomal ALA gel 3% “as is,” however, test results were negative. Furthermore, they had negative results to patch testing with the regularly used disinfectants, hand soaps, and nitrile gloves as well as the baseline series, topical ingredient series, preservative series, and disinfectant series of the German Contact Dermatitis Research Group (DKG). Thereby, only a positive reaction to povidone iodine was observed to which the patient was not regularly exposed.

DISCUSSION

Both of our patients were sensitized to MAL, the active ingredient of Mevix. The follicular reaction to Ameluz in patient 1 could be



FIGURE 1 Patch test reading of patient 2 on day 2. Left: 13 excipients of Metvix vehicle (see rows 1–13 in Table SS1); right: 1) Metvix 50% pet., 2) Ameluz 50% pet., 3) liposomal 5-aminolevulinic acid gel 3%, 50% pet., 4) methyl 5-aminolevulinate hydrochloride

interpreted as irritant. Frequent irritant reactions to Ameluz especially in higher concentrations have been described in patch tests of control patients.¹ There is no indication for a cross-allergy between MAL and ALA in our patients, which is consistent with findings in small studies.^{4,8} It is suspected that the methyl group in MAL may be responsible for the higher risk of sensitization compared with ALA.⁹

According to information provided by the manufacturer, tolerance studies in humans showed contact sensitization in 52% of 58 healthy volunteers after a total of nine applications of Metvix over the course of 3 weeks, while patch testing of 21 patients after at least four PDT treatments with Metvix showed contact sensitization in only 14%.¹⁰ While the healthy volunteers received applications three times per week, the interval between applications in patients receiving regular PDT treatment is usually at least a few weeks if not month or years and therefore much longer. This could indicate that a higher frequency of exposure may result in a higher risk of sensitization.

Over the years several reports on patients with allergic contact dermatitis caused by MAL have been published.^{1–6} The symptoms described include aggravated and spreading local inflammatory reactions such as prolonged eczematous reactions, massive edema or blistering as well as generalized rashes. In some cases treatment with systemic corticosteroids was necessary.^{3,4} Studies estimate a sensitization risk to Metvix between 0.4% and 3% for patients.^{4,6,8} However, only a small fraction of patients treated with PDT receives patch testing and symptoms of allergic contact dermatitis may easily be mistaken for the expected phototoxic reaction. Therefore, the true sensitization risk for patients is probably much higher.

In 2011 Pastor-Nieto et al reported the first case of allergic contact dermatitis caused by occupational exposure to MAL.⁷ In their report, the 49-year-old woman suffered from itchy, erythematous lesions on the eyelids and fingertips while working with MAL 1 day per week. The symptoms started a few months after first exposure and resolved completely after termination of exposure. In contrast to our patients, gloves were not used regularly while working with MAL. When analyzing our patients' work processes in detail we found out

that skin contact with MAL most likely occurs due to handling of the same Metvix tubes and packings both with gloves and bare hands afterwards.

Only one of our patients had clinically relevant contact sensitization in terms of hyperkeratotic-fissured hand eczema (patient 1). She may have been more prone to the development of symptoms owing to her longer seniority in the field of PDT, her history of hand eczema as well as her multiple known contact allergies. Her current symptoms may also have been a combination of allergic contact dermatitis and irritant dermatitis due to working with gloves and disinfectants.

In conclusion, we would like to point out that sensitization to MAL and resulting allergic contact dermatitis is not only an important adverse event in patients receiving repetitive PDT treatment but also in individuals with occupational exposure. The sensitization risk may even be higher than in patients considering the high frequency of exposure over a long period. The occurrence of two cases of sensitization to MAL out of three assistants in the same PDT department also emphasizes considerable risk. Moreover, occupational sensitization may even result in inability to work, while patients can easily receive alternative therapies including ALA PDT most of the time.

CONFLICTS OF INTEREST

P.G. has received honoraria for lectures/presentations from Galderma and Biofrontera.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Online supplemental Table 1. Patch test readings at day 1, day 2 and day 3.

Allergen	patient 1			patient 2		
	D1	D2	D3	D1	D2	D3
Self-emulsifying glycerol monostearate	-	-	-	-	-	-
Cetearyl alcohol	-	-	-	-	-	-
Polyoxyl 40 stearate (=Macrogol 2000)	-	-	-	-	-	-
Metyl paraben	-	-	-	-	-	-
Propyl paraben	-	-	-	-	-	-
Disodium EDTA	-	-	-	-	-	-
Glycerol	-	-	-	-	-	-
Petrolatum	-	-	-	-	-	-
Cholesterol	-	-	-	-	-	-
Isopropyl myristate	-	-	-	-	-	-
Peanut oil	-	-	-	-	-	-
Almond oil	-	-	-	-	-	-
Oleyl alcohol	-	-	-	-	-	-
Metvix 50% pet.	+	++	++	++	++	++
Ameluz 50% pet.	-	f	f	-	-	-
liposomal ALA gel 3%, 50% pet.	-	-	-	-	-	-
Methyl 5-aminolaevulinate hydrochloride	+	++	++	+	++	++

-, negative; +, weak positive; ++, strong positive; f, follicular.