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**Allergic contact dermatitis to topical pro-drugs used in photodynamic therapy**

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## **Introduction**

Topical photodynamic therapy (PDT) is a well-established treatment for actinic keratosis, Bowen's disease and superficial basal cell carcinoma and its use has also been explored for a variety of other indications.<sup>1,2,3</sup> Treatment involves application of a pro-drug (either 5-aminolaevulinic acid (ALA) or its methyl ester, methylaminolevulinate (MAL)) which is preferentially taken up by dysplastic or neoplastic cells and converted into the active photosensitiser protoporphyrin IX (PPIX).

Subsequent activation of PPIX by red light results in the production of cytotoxic oxygen species, inflammation and relatively selective diseased tissue destruction.

A degree of erythema, oedema and crusting is to be expected during and after photodynamic therapy, although this is usually a localised phototoxic reaction with a predictable time course. A far less common adverse effect is the development of a more severe dermatitis reaction as a consequence of contact allergy to the pro-drug used. This phenomenon has previously been described in case reports and case series,<sup>4,5,6</sup> but is not widely documented and we report our experience in the Scottish PDT centre.

## **Materials and methods**

The dermatology PDT service was commenced in 1998 and treatment was undertaken using an ALA preparation (5-ALA, 20%, Mandeville Medicines) as the pro-drug in all patients until 2008 when a licensed preparation of MAL (Metvix®, 16%, Galderma, UK) was introduced for use in actinic keratosis, Bowen's disease and superficial basal cell carcinoma and subsequently was used in the majority of our cases. An ALA containing nanoemulsion (Ameluz®, 7.8% gel, Biofrontera) has since been licensed for the treatment of actinic keratosis and has been used in the department since 2014 to treat selected patients.

Over a 17 year period we have identified 14 patients (out of 1532 treated (0.91%)) who experienced severe blistering and/or prolonged eczematous reactions following PDT and an allergic contact dermatitis to ALA or MAL was suspected on clinical grounds. Of the 14 patients, nine were

female and the median patient age was 71 (range 53-82) years. All of the patients had multiple areas of actinic keratosis, Bowen's disease or superficial basal cell carcinoma which had been treated with conventional PDT, the median number of areas treated was 8 (range 3-25). All patients had also received multiple PDT treatment sessions, with a median of 7 (range 3-21 sessions) and 2 patients had also received daylight PDT on 2 and 3 occasions.

Eight patients underwent PDT exclusively with MAL (Metvix®, 16%, Galderma, UK), two patients exclusively with ALA (5-ALA, 20%, Mandeville Medicines), two patients with both Metvix® and 5-ALA, 20%, one patient with both Metvix® and ALA (Ameluz®, 7.8% gel, Biofrontera) and one patient with all three of the topical pro-drugs.

Patch testing was performed to Metvix® in all 14 patients. Ten patients were also patch tested to ALA, 20% and 11 patients were patch tested to Ameluz®. As the patients were generally elderly, often frail and found extra hospital visits difficult, a patch test procedure using Finn Chambers® was carried out with allergens applied for 48 hours and readings performed only at 96 hours, at a time-point when early irritant toxic reactions would usually have resolved, apart from at high concentration of pro-drug preparation, but allergic reactions would persist. We also wanted to minimise any light exposure to the back incurred by multiple interventions and patients were advised to protect the sites on the back from any natural or artificial light throughout the procedure. The development of erythema, oedema and/or vesicles within the test area was considered a positive result. Rim effect erythema only was considered to be an irritant reaction and therefore not of significance.

Patch testing was performed to 10%, 5%, 1%, 0.5% and 0.1% ALA (ALA, 20%) cream in white soft paraffin (WSP). Metvix® patch testing was performed in all patients using 10%, 5%, 1%, 0.5%, 0.1% dilutions, in WSP. Ameluz® testing was to 7.8%, 3.9%, 1.6% and 0.78% in WSP.

## Results

Ten of the 14 patients (71%) had positive readings on patch testing consistent with the diagnosis of an allergic contact dermatitis. Three patients demonstrated positive reactions to all three topical pro-drug preparations suggestive of cross reactivity. Of the four patients with negative patch testing, two had irritant rim reactions to ALA (20%) and Ameluz®, which were not considered significant.

Patch testing was not performed to product excipients.

### Table 1

Patch testing to Metvix® and Ameluz® was performed in six control subjects and none had positive reactions at 96 hours, although three did develop irritant reactions (rim effect) only to the higher concentrations of Ameluz®.

## Discussion

The 10 patients who demonstrated positive reactions on patch testing represent 0.65% (10/1532) of those treated with PDT between 1998 and 2015. Although the higher concentrations of Ameluz® caused irritant rim effect reactions in 50% (3/6) of control subjects, we considered that the positive reactions in the 10 patients were representative of true allergy given the appearance and morphology of the reactions and the late 96 h time-point of readings, at which point most irritant reactions, particularly at lower concentrations of pro-drug preparation, would be expected to have resolved. We did not perform patch testing to product excipients, so although we consider that this is most likely allergy to ALA and/or MAL, we were unable to prove this definitively. However in support of this, patch testing to the base creams, without the active components (ALA and MAL), has been performed in a previous study in patients similarly considered to have suspected allergy and positive reactions to the pro-drugs occurred, whilst testing to the base preparations was negative.<sup>4</sup>

Although uncommon, we wish to highlight contact allergy to the pro-drug preparations used in PDT as an important adverse event as it may easily be mistaken for a severe phototoxic reaction. Patients

who have contact allergy should not receive further exposure to the culprit pro-drug due to the risk of a generalised dermatitis.<sup>5</sup> In some cases it may be possible to use an alternative pro-drug as cross reaction, whilst likely, is not invariably present. In our experience the patients most at risk of sensitisation are those with multiple lesions and/or large treatment areas and those who have received multiple treatments. We would thus advise that clinicians have a low threshold for patch testing when patients present with unusually severe, eczematous or prolonged reactions to PDT.

### **Acknowledgements**

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