Aspects of fluorescence diagnostics and photodynamic therapy in non-melanoma skin cancer.

Akademisk avhandling

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av

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This thesis is based on the following papers, which are referred to in the following text by their corresponding Roman numerals:

I. Ericson MB, Sandberg C, Stenquist B, Gudmundson F, Karlsson M, Ros A-M, Rosén A, Larkö O, Wennberg A-M and Rosdahl I. Photodynamic Therapy of Actinic Keratosis at Varying Fluence Rates: Assessment of Photobleaching, Pain and Primary Clinical Outcome. *Br. J. Dermatol.,* 2004; **151:**1204-12.

II. Sandberg C, Stenquist B, Rosdahl I, Ros A-M, Synnerstad I, Karlsson M, Gudmundson F, Ericson MB, Larkö O and Wennberg A-M. Important factors for pain during photodynamic therapy for actinic keratosis. *Acta Derm. Venereol.,* 2006; **86**:404-8.

III. Sandberg C, Halldin C, Ericson MB, Larkö O, Krogstad AL, Wennberg A-M. Bioavailability of aminolaevulinic acid and methyl-aminolaevulinate in basal cell carcinomas - a perfusion study using microdialysis *in vivo. Br. J. Dermatol.,* 2008 Nov **159(5)**:1170-1176, E-pub 2008, Aug 19.

IV. Sandberg C, Paoli J, Gillstedt M, Halldin CB, Larkö O, Wennberg A-M and Ericson MB. Fluorescence diagnostics in connection to photodynamic therapy with a comparison of methyl-aminolevulinate and aminolevulinic acid. Submitted for publication

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ABSTRACT

Photodynamic therapy (PDT) is now an established method to treat superficial basal cell carcinoma (BCC), Bowen's disease (BD) and actinic keratosis (AK). The main advantage of PDT is that it is non-invasive and gives excellent cosmetic results; although the majority of the patients do experience some degree of pain, which can sometimes be extreme. Fluorescence diagnostics (FD) is a method to diagnose mainly BCC, which is the most common type of tumour within the class of non-melanoma skin cancer (NMSC) and accounts for about 80% of all skin tumours. This technique can be used as an *in vivo* pre-surgical diagnostic tool, which can help to detect occult tumour borders of ill-defined BCCs.

In the first study (Paper I), the impact of fluence rate and spectral range on the primary treatment outcome and bleaching rate in AKs using aminolaevulinic acid (ALA)-PDT was studied. Pain during treatment was also registered. The results imply that the photobleaching rate and primary treatment outcome were dependent on the fluence rate and that a low fluence rate (30 mW/cm^2) appears preferable. In the second study (Paper II), risk factors related to pain during PDT for AK were investigated. The most important factors relating to the experience of pain seem to be the size and "redness" of the lesion. No significant pain relief with capsaicin was seen. In the third study (Paper III), the transdermal penetration of ALA and methyl-aminolaevulinate (MAL) *in vivo* were investigated using a microdialysis technique. The results imply that there is no significant difference in transdermal penetration of ALA and MAL in tumour tissue. Detectable levels of the drug were not obtained in almost 50% of the lesions where catheters were inserted 1-1.9 mm into the lesion. Curettage was not found to affect the interstitial concentration, indicating that penetration of the drug might indeed be a problem when treating BCCs thicker than 1 mm. In the final study presented within this thesis (Paper IV), the fluorescence contrast in patients undergoing MAL-PDT for superficial BCCs was evaluated. The MAL fluorescence contrast obtained between the tumour and normal skin was also compared to that obtained in a previous study using ALA. In both cases it was possible to identify areas in the fluorescence images corresponding to a tumour and to surrounding normal skin. The mean fluorescence contrast with MAL, however, was significantly higher than the mean fluorescence contrast after application of ALA. Thus, MAL generally renders a higher tumour contrast compared to ALA in superficial BCCs. No correlation between fluorescence and treatment response could be observed.

The results of this thesis prove that PDT, using either ALA or MAL, is effective in the treatment of thin non-melanoma skin cancer and pre-cancer. These results further suggest that lower fluence rate should be considered as a precaution to minimise pain response when treating large and inflammatory lesions, although more study is needed. When performing FD, MAL is the best option and lack of treatment response cannot be connected to fluorescence but maybe due to the fact that the pro-drug does not successfully penetrate into the deeper parts of the tumour.

***Key words*:** actinic keratosis, aminolaevulinic acid, fluorescence contrast, methyl-aminolaevulinic acid, microdialysis, non-melanoma skin cancer, pain, photodynamic therapy

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