Pain Associated with Photodynamic Therapy: Mechanisms and Pain-reducing Techniques

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Stine Regin Wiegell, MD, conducted her PhD thesis at the Department of Dermatology, Bispebjerg Hospital, Copenhagen University Hospital, Denmark during 2001 and from 2005 through 2008. The academic advisor was Professor Hans Christian Wulf, DSc. The opponents were: Ann-Marie Wennberg, DSc, Gothenburg, Sweden; Trond Warloe, PhD, Oslo, Norway; and Gregor Jemec, DSc, Roskilde Hospital, Denmark.

Pain during illumination is the only acute severe adverse event associated with photodynamic therapy (PDT), which otherwise is a very attractive treatment for non-melanoma skin cancer and other skin diseases. The aim of the thesis was to study PDT-induced pain and document ways to reduce the pain.

A randomized double-blinded study was performed, comparing pain experience in normal tape-stripped skin treated with 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) and methyl aminolaevulinate-based photodynamic therapy (MAL-PDT) (1). The results showed that MAL-PDT was less painful than ALA-PDT performed on normal skin in 20 healthy volunteers. Since MAL induced less protoporphyrin IX (PpIX) fluorescence and resulted in fewer skin reactions after PDT than ALA a second randomized double-blinded study was performed in diseased skin (2). Fifteen patients with acne vulgaris were treated split-face with ALA on one side and MAL on the other. MAL-PDT and ALA-PDT was equally painful during illumination, but ALA-PDT resulted in more prolonged and severe adverse effects after treatment.

The association between pain during illumination and PpIX fluorescence was evaluated (3). Twenty-six patients with actinic keratoses (AK) in different localizations and 34 patients with facial acne vulgaris were treated with MAL-PDT. It was found that pain during PDT correlated with the PpIX fluorescence in the treatment area prior to illumination. The second treatment was less painful than the first and PDT of AK located on the extremities was less painful than treatment of AK lesions in the face and scalp. These reductions in pain correlated with a lower PpIX fluorescence.

Several interventions have been tried in an attempt to reduce pain during PDT. The effect of fluence rate on PDT-induced pain was evaluated (3) and the pain-relieving effect of cooling and pauses during illumination investigated (4). It was found that a reduction in the fluence rate from 68 mW/cm^2 to 34 mW/cm^2 resulted in a decrease in pain during PDT of facial acne vulgaris.

Fig. 1. Stine Regin Wiegell (*second from left*) defended her PhD thesis on pain and photodynamic therapy in the University of Copenhagen, Denmark. The opponents were Ann-Marie Wennberg (*left*), Gothenburg, Sweden; Trond Warloe (*middle*), Oslo, Norway; and Gregor Jemec, (*right*), Roskilde, Denmark. Her supervisor was Professor Hans Christian Wulf (*second from right*).

Cooling during illumination resulted in a minor reduction in pain intensity during PDT of 24 patients with AK. Moreover, a 3-minute pause half-way through illumination reduced the pain considerably.

It is of great importance to find better pain-relieving strategies for patients undergoing PDT. Daylight-mediated PDT might be such a strategy, being an effective and very convenient way to solve the problem of PDT-induced pain.

List of original publications

1. Wiegell SR, Stender I-M, Na R, Wulf HC. Pain associated with photodynamic therapy using 5-aminolevulinic acid or 5-aminolevulinic acid methylester on tape-stripped normal skin. Arch Dermatol 2003; 139: 1173–1177.