Photodynamic Therapy for the Dermatologist

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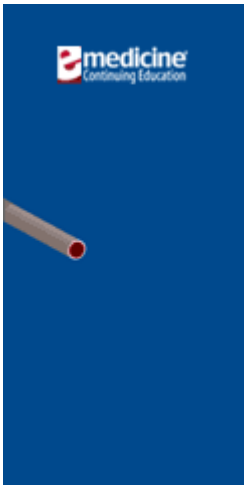

Photodynamic therapy (PDT) involves the use of photochemical reactions mediated through the interaction of photosensitizing agents, light, and oxygen for the treatment of malignant or benign diseases. PDT is a 2-step procedure. In the first step, the photosensitizer is administered to the patient by one of several routes (eg, topical, oral, intravenous), and it is allowed to be taken up by the target cells. The second step involves the activation of the photosensitizer in the presence of oxygen with a specific wavelength of light directed toward the target tissue. Because the photosensitizer is preferentially absorbed by hyperproliferative tissue and the light source is directly targeted on the lesional tissue, PDT achieves dual selectivity, minimizing damage to adjacent healthy structures.

This article provides an update on PDT for the practicing dermatologist by discussing each of the essential components in sequence: mechanisms of action, common photosensitizers, typical light sources, and applications. Although various PDT photosensitizers have been studied in dermatology, this article focuses on the uses of topically applied aminolevulinic acid (ALA) and methylaminolevulinate (MAL).

Most cells of the human body can transform ALA or MAL into porphyrins. However, significant differences exist in porphyrin accumulation between various tissues and cell types. After the application of MAL or ALA to human skin, porphyrins accumulate mostly in sebaceous glands and the epidermis. Neoplastic cells accumulate more porphyrins than normal cells, which has prompted the development of ALA and MAL PDT for the treatment of actinic keratoses (AKs), Bowen disease, and basal cell carcinoma (BCC).

Light at a wavelength corresponding to a peak of the porphyrin excitation spectrum in tissues is used to most efficiently generate a therapeutic effect. The Soret band (approximately 405-420 nm) is the most important excitation peak of protoporphyrin IX and is included in the spectral output of the US Food and Drug Administration (FDA)–approved Blu-U device, which is used with ALA. Another peak in the excitation spectrum of porphyrins includes a red peak at approximately 635 nm, which is targeted by different devices, including those approved to be used with MAL.

Following blue or red light activation, porphyrins are excited to a higher energy triplet state, which can either emit light (fluorescence) or generate reactive oxygen species, such as singlet oxygen or free radicals. The generation of singlet oxygen species, labeled type 2 photochemical reactions, are believed to predominate in PDT. Because singlet oxygen does not travel very far within a cell, the molecular effects are influenced by the intracellular localization of the photosensitizer at the time of light exposure. Porphyrins derived from ALA are mainly localized in the vicinity of mitochondria, which can lead to apoptosis or necrosis of malignant cells upon light exposure. Both phenomena have been

shown to be induced following ALA PDT.

For the treatment of acne, preferential targeting of sebaceous glands and *Propionibacterium acnes* reduction are believed to be the main mechanisms involved. Because *P acnes* has been shown to naturally accumulate porphyrins, blue or red light alone can also have a direct therapeutic photodynamic effect on the bacteria. The exact mechanisms involved in ALA PDT for the treatment of photoaging are not well known, but increased collagen synthesis has been demonstrated following ALA PDT.

Beyond direct phototoxic effects on target tissue, PDT with various photosensitizers has been shown to modify cytokine expression and induce immune-specific responses. Immunologic effects include the production of interleukin 1-beta, interleukin 2, tumor necrosis factor-alpha, and granulocyte colony-stimulating factor. PDT generally has a low potential for causing DNA damage, mutations, and carcinogenesis.

The most commonly used photosensitizers are ALA and MAL. Both ALA and MAL are approved in several countries, including the United States, for the treatment of AKs only. However, off-label uses such as the treatment of BCC, photoaging, and acne vulgaris are common. Each photosensitizer is discussed below.

5-Aminolevulinic acid

ALA is currently available in a prepackaged plastic tube containing 2 sealed glass ampules, 1 with the ALA powder and the other with the hydroalcoholic solution (Levulan). The vehicle ampule contains 1.5 mL of solution composed of ethanol (48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of ALA hydrochloric acid as a dry powder. The applicator tube is enclosed in a protective cardboard sleeve with a cotton applicator. These Levulan Kerasticks are available in boxes of 6.

The topical solution (final ALA concentration of 20%) must be prepared just prior to application by breaking the glass ampules with gentle pressure and subsequently mixing the contents by shaking the applicator. Care must be taken to break the 2 ampules well before application.

The only approved indication for ALA (ie, in the United States and Canada) is for the treatment of hypertrophic AKs of the face and scalp.

Methylaminolevulinate

MAL is available in a cream containing 168 mg/g of MAL (final MAL concentration of 16.8%), glyceryl monostearate, cetostearyl alcohol, polyoxyl stearate, methylparaben, propylparaben, disodium edetate, glycerin, white

petrolatum, cholesterol, isopropyl myristate, refined peanut oil, refined almond oil, oleyl alcohol, and purified water. The trade name for this product is Metvix, except in the United States, where it is called Metvixia.

MAL cream is packaged in an aluminium tube containing 2 g of cream. A tube should be used within 1 week after opening. MAL cream should be stored at 2-8°C (35.6-46.4°F).

MAL is currently approved in the United States for the treatment of nonhyperkeratotic AKs of the face and scalp in immunocompetent patients. As of April 27, 2006, MAL was not yet commercially available in the United States. MAL is also approved in several European countries, New Zealand, and Australia for superficial and/or nodular BCC unsuitable for other available therapies because of possible treatment-related morbidity or a potentially poor cosmetic outcome. MAL has also been recently approved in Europe for squamous cell carcinoma (SCC) in situ (Bowen disease) when surgical excision is considered less appropriate. The exact indication varies according to country.

Any light source, either laser or nonlaser, with suitable spectral characteristics and a high output at an absorption maximum of the photosensitizer can be used for PDT.

Lasers

The purpose of lasers in PDT is to initiate photochemical reactions in contradistinction to their photothermal or photomechanical effects, as are seen in other dermatologic uses. Almost any laser with an output wavelength within the visible spectrum (400-800 nm) may be used to activate ALA and MAL, although efficiency may be compromised if the output wavelength does not approximate the spectral absorption peak of the photosensitizer.

Laser PDT has many advantages. First, the monochromaticity of lasers provides maximum effectiveness if the wavelength of the laser corresponds with the peak absorption of the photosensitizer. Second, lasers can produce high irradiance to minimize the therapeutic exposure time. Finally, lasers can be readily coupled to fiberoptics, enabling light delivery to any organ, such as the bladder, gastrointestinal tract, or lungs. On the other hand, lasers in PDT are not without their limitations. The lasers are relatively expensive, they require special maintenance, and, when coupled with fiberoptics, they may only be used only small skin lesions.

Noncoherent light sources

In the treatment of large skin lesions, noncoherent light sources are superior to laser systems because of their large illumination fields. Other advantages of noncoherent light sources are their low cost, smaller size, and ready availability. Additionally, polychromatic light sources allow the use of different photosensitizers with different absorption maxima. Given the right dose of drug and light, noncoherent light sources appear to be every bit as effective as laser sources.

Light sources for ALA and MAL

In current dermatologic use, the most widely accepted application of ALA PDT is with blue light for the treatment of AKs. FDA-approved blue light sources include the Blu-U and ClearLight systems.

MAL PDT involves exposure to 37 J/cm^2 or 75 J/cm^2 of red light using the Aktilite or the Curelight device, respectively. Only the Curelight is currently FDA approved. However, the Aktilite is the most widely used device in Europe.

The only FDA-approved indication for ALA PDT and MAL PDT in dermatology is currently the treatment of AKs. Common off-label uses include the treatment of BCC, photoaging, acne vulgaris, and Bowen disease. Less common off-label indications are possible.

Actinic keratoses

Both ALA and MAL are approved in several countries, including the United States (by the FDA), for the treatment of AK. In the FDA-approved protocol, ALA is to be applied on AKs only, followed 14-18 hours later by 10 J/cm^2 of blue light exposure using the Blu-U device. In phase 3 studies, lesions of 243 patients were treated once with ALA PDT and were re-treated at 8 weeks if they did not show a complete response. The complete clinical response of individual lesions at week 12 was 91%, with just one ALA-PDT session. The percentage of patients who had a complete response with all lesions was 73% at week 12. However, in clinical practice, most physicians are currently using shorter (30-90 min) incubation times for the treatment of AK. This short incubation period has not yet been approved by regulatory authorities.

Although the FDA-approved protocol involves the application of ALA only on individual lesions, many physicians are now using broad applications on facial areas where multiple ill-defined AKs or concomitant photoaging is present. This has the theoretical advantage of treating subclinical precancerous lesions. In studies using the hairless mouse as a model, multiple broad-area ALA and MAL applications followed by light exposure have been shown to delay the appearance of AK and SCC. If broad-area application is used, clinicians should be careful when using intervals of longer than 1 hour between drug application and light exposure. The phototoxic reaction (erythema, crusting) observed after ALA and MAL is significantly stronger with longer exposure time.

Physicians are also currently using light sources other than the FDA-approved Blu-U for the treatment of AK. These include intense pulsed light and pulse dye laser. Limited data are available on the efficacy of these light sources combined with ALA for the treatment of AK.

For the treatment of AK with MAL, the cream is applied on lesions following skin preparation. Skin preparation consists of removal of the crusts or hyperkeratotic portion of the AK with a curette, which probably enhances MAL penetration. MAL is then applied under occlusion for a period of 3 hours, followed by exposure to 37 J/cm^2 or 75 J/cm^2 of red light using the Aktilite or the Curelight device, respectively. Only the Curelight is currently approved by the FDA; however, the Aktilite is the most widely used device in Europe. The European labeling suggests using a single MAL-PDT session, although this can be repeated 3 months later for lesions that did not completely respond. The FDA-

approved protocol suggests using 2 MAL-PDT sessions conducted 7 days apart.

A multicenter randomized study comparing the efficacy of 2 MAL-PDT treatments 7 days apart with a single treatment, followed by re-treatment at 3 months for lesions that did not exhibit a complete response, showed that both regimens were equally effective. However, subanalysis of the data suggested that a single session (without re-treatment) may not be sufficient for AKs that are of moderate thickness.

For more detailed information on ALA PDT and MAL PDT for AKs, see Therapeutic Guidelines for AK Treatment.

Basal cell carcinoma

A number of small studies have been published using ALA PDT for the treatment of BCC. However, these studies used varying ALA formulations, concentrations, penetration enhancers, light sources, and time between ALA application and light exposure. These studies have shown short-term complete response rates ranging from 59-92% and recurrence rates ranging from 5-44%, with a tendency towards lower clearance rates for nodular BCC. These variations in response are probably related to the different protocols and techniques used. Therefore, clinicians should be cautious when using ALA for the treatment of BCC, especially nodular BCC, given that this is not an approved indication, with no large long-term studies on the efficacy of this treatment with the currently available ALA formulation.

Only MAL has been studied with standardized protocols in phase 3 multicenter trials for the treatment of BCC. Both the Curelight and the Aktilite devices have been used in these studies. In all these studies, a gentle curettage was performed to remove crusts before MAL application.

Studies show histological cure rates at 3 months to be 85% for superficial BCC and 75% for nodular BCC. At 24 months after treatment, lesion recurrence rates (recurrence in lesions that initially showed a complete response) have been reported to be 18%. Five-year follow-up data recently presented at meetings show that most recurrences following MAL PDT for superficial or nodular BCC occur during the first 2 years after PDT. A consistent finding in MAL-PDT studies for BCC is that the cosmetic outcome has been shown to be superior to surgery or cryotherapy.

Photoaging

Large-surface ALA PDT with the Blu-U or intense pulsed light devices for the treatment of photoaging is not currently approved by the FDA, but it is widely used by dermatologists. At present, the optimum parameters for the treatment of photoaging with ALA are unknown. Variations in the number of sessions and in the device, filters, fluence, irradiance, and frequency used could all have a significant impact on efficacy. MAL also has the potential to improve photoaging; however, MAL PDT for photoaging is only starting to be used in Europe and efficacy data are lacking.

Acne vulgaris

ALA PDT is currently used off-label for the treatment of acne. Significant clinical improvement and a decrease in sebum production and sebaceous gland size have been shown posttreatment. Histological analysis showed destruction of sebaceous glands, which suggests that this therapy has the potential for long-term improvement of acne. Additional small studies using various light sources, including the Blu-U and intense pulse light, have also been published and suggest that ALA PDT has

efficacy for the treatment of acne.

Physicians currently using ALA PDT for the treatment of acne use a short incubation time of 30-60 minutes followed by light exposure, mostly from a Blu-U or an intense pulse light device. Pulse dye lasers can also be used, although the spectral output of the pulse dye laser is not ideal to match the excitation spectrum of protoporphyrin IX. Multiple sessions may provide a better improvement; however, the exact frequency and number of sessions required to optimize the treatment is currently unknown. The importance of using red versus blue light has not been thoroughly studied, but given that sebaceous glands are often located in the mid dermis, red light might be a better choice to target these glands.

Bowen disease

Both ALA and MAL have been shown to induce good clinical responses in persons with Bowen disease (SCC in situ). MAL has just recently been approved in Europe for the treatment of Bowen disease when surgical excision is considered less appropriate. Bowen disease might be one of the best clinical indications for PDT because the lesions often are large and the surgical approach may result in extensive scarring.

Other applications

ALA PDT using a 595-nm pulse dye laser has been reported to induce a better response than pulse dye laser therapy alone in the treatment of sebaceous hyperplasia in a pilot study with 10 patients. A number of anecdotal descriptions of using ALA PDT for various other skin diseases have also been reported, but these are beyond the scope of this article.