Protection Afforded by Sunscreens Containing Inorganic Sunscreening Agents Against Blue Light Sensitivity Induced by Aminolevulinic Acid

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BACKGROUND Application of aminolevulinic acid (ALA) for photodynamic therapy induces significant sensitivity to visible light.

OBJECTIVE To determine whether sunscreens containing inorganic agents are effective against sensitivity to blue light induced by ALA application.

METHODS & MATERIALS Twenty subjects received application of ALA on the arm. Thirty minutes before blue light exposure, two sun protection factor 50 inorganic-based sunscreens containing iron oxide 3.2% and 0.2% were applied on separate areas where ALA was applied; a third area received no sunscreen. Small areas of skin were exposed to increasing fluences of blue light 3 or 18 hours later, and the minimal phototoxic dose (MPD) was noted.

RESULTS Three hours after ALA application MPD was 29.2 and 22.6 J/cm² for skin protected with sunscreen containing iron oxide 3.2% and 0.2%, respectively, and 10.6 J/cm² for unprotected skin (p = .003 and .0497 respectively). At 18 hours after ALA application, MPD for sunscreen containing iron oxide 3.2% was 5.78, compared with 0.33 for unprotected skin (p < .001) with a blue light protection factor of 21.

CONCLUSION The sunscreen containing iron oxide 3.2% afforded significant protection against blue light sensitivity induced by ALA application.

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ganic-based sunscreens can protect against visible-light sensitivity induced by topical application or ALA or MAL, but to our knowledge, this has never been studied.13,14

The purpose of the current trial was to assess the ability of 2 sunscreens containing inorganic sunscreening agents to protect against sensitivity to blue light induced by topical application of amino-levulinic acid.

Materials and Methods
Eleven male and 9 female subjects (aged 24 to 62; mean 46.6) with phototype II or III were included in the study. The study was conducted according to the 1996 ethical guidelines of the Declaration of Helsinki. Informed consent was obtained before any study-related procedures were performed, and an independent ethics committee approved the study. This study was performed in two subsequent parts, each involving 10 subjects.

Two sunscreens were tested. Sunscreen A was a sun protection factor (SPF) 50 very high protection cream (Avene 50 creme minérale) containing titanium dioxide 11%, zinc oxide 2.4%, and iron oxide 0.2%. Sunscreen B was a SPF 50 very high protection tinted compact (Avene 50 compact) with a paste texture containing titanium dioxide 15%, zinc oxide 6.8%, and iron oxide 3.2%. Laboratoires Dermatologiques Avene, France, provided both sunscreens.

Exposure 3 hours after ALA Application
In the first part of the study 20% ALA in a hydroalcoholic vehicle (Levulan, Coherent-AMT, Toronto, Canada) was applied to 10 subjects on a 10- × 15-cm area of normal skin on the inner aspect of the arm after cleaning with acetone. Two hours and 30 minutes later, Sunscreen A and Sunscreen B were applied at a dose of 2 mg/cm² on 2 separate 3.33- × 15-cm areas on the arm where ALA had been applied. A third 3.33- × 15-cm zone where ALA had been applied did not receive sunscreen application or any other treatment.

Three hours after ALA application, 1- × 1-cm² squares of skin on the arm that received ALA were exposed to 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 J/cm² of blue light generated by a Blue-U unit (DUSA Pharmaceuticals, Wilmington, MA). The irradiance of the blue light source was 10 mW/cm². Subjects were instructed not to expose their arm to the sun or intense light for 24 hours. Subjects were evaluated 24 hours after light exposure, and the presence or absence of erythema was recorded for every 1- × 1-cm² area exposed to blue light for unprotected skin, as well as skin protected with each of the 2 sunscreens. The minimum phototoxic dose (MPD) was defined as the lowest light fluence that induced the presence of erythema and was recorded for unprotected skin and skin protected with Sunscreen A and Sunscreen B.

Exposure 18 hours after ALA Application
For the second part of this study, ALA was also applied on a 10- × 15-cm area of normal skin on the inner aspect of the arm to an additional cohort of 10 different subjects under conditions identical to the first 10 treated subjects. Subjects were then instructed to go home and not to wash their arm until the next visit. Seventeen hours and 30 minutes after ALA application, the 2 sunscreens were applied on the area where ALA was applied in the same manner as in the first part of this study. Eighteen hours after ALA application, the arm was exposed to blue light under conditions similar to the first part of the study with the addition of a 1- × 1-cm² area of skin that was exposed to 32 J/cm² for the 3 studied areas. Subjects were evaluated 24 hours after exposure as in part A.

Statistical Analysis
For each subject, the mean MPD for unprotected skin and skin protected by Sunscreen A and Sunscreen B was calculated. For subjects in the first part of this study who failed to exhibit any erythema
even at the highest fluence, a value of 32 J/cm² was assigned for mean MPD calculation because fluences tested increased in a geometric manner. MPD of unprotected skin and skin protected with Sunscreen A and Sunscreen B was compared using the Wilcoxon rank sum test. The blue light protection factor was calculated for each sunscreen by averaging the individual ratios of MPD for unprotected skin:MPD of skin protected with sunscreen.

Results

Exposure 3 hours after ALA Application

All 10 subjects completed the protocol. Three subjects complained of a mild burning sensation during light exposure, 2 of a tingling sensation, and one of pruritus during light exposure. These sensations were mild and were judged to be associated with blue light exposure after ALA application and not to sunscreen application. Because the squares were close together, it was not possible for subjects to assess which squares caused these sensations.

Nine subjects presented erythema 24 hours after exposure on at least one square (at least one fluence) for the non-protected skin, 4 for the skin protected with Sunscreen A, and 1 for the skin protected with Sunscreen B. The single subject who showed erythema on the skin protected with Sunscreen B showed erythema on the 4-J/cm² square but not on the 8 and 16-J/cm² squares. Three hours after ALA application, mean MPD ± standard deviation was 10.6 ± 8.85, 22.6 ± 12.58, and 29.2 ± 8.85 J/cm² for unprotected skin and skin protected with Sunscreen A and Sunscreen B, respectively. The difference between the MPD of skin protected with Sunscreen B and Sunscreen A and that of nonprotected skin was statistically significant (p = .003 and .0497, respectively).

Exposure to Blue Light 18 hours after ALA Application

Ten subjects were treated with blue light and one failed to complete the study. He had moderate back pain after a fall on ice, which was considered unrelated to the study, and he could not come to the clinic 24 hours after light exposure for skin evaluation. Another subject presented a mild confluent erythema on all areas where ALA was applied. This was noted on the day ALA was applied and was evaluated to be related to the ALA application technique (acetone cleaning and application of ALA in a hydroalcoholic solution). All subjects presented erythema on at least one exposed zone for nonprotected skin, skin protected with Sunscreen A, and skin protected with Sunscreen B (Figure 1).

Eighteen hours after ALA application, the mean MPD ± standard deviation for nonprotected skin and skin protected with Sunscreens A and B was 0.33 ± 0.13, 0.81 ± 1.22, and 5.78 ± 4.74 J/cm², respectively. The difference in MPD between sunscreen-protected skin and nonprotected skin was statistically significant for Sunscreen B (p < .0001) but was not statistically significant for skin protected with Sunscreen A (p = .48). The blue light protection factor was 21 for Sunscreen B and 2 for Sunscreen A.

Discussion

Topical application of ALA or MAL induces synthesis and accumulation of porphyrins predominantly in the epidermis, hair follicle epithelium, and sebaceous glands. Peak fluorescence after ALA
application is 12 hours in perilesional skin, with a mean clearance half life of 28 hours (Levulan product monograph). Peak fluorescence after MAL application on forearms occurs 1 hour after cream removal, and phototesting showed that 6 of 16 subjects were still sensitive to visible light 24 hours after MAL application.\textsuperscript{15} The excitation spectrum of porphyrins is mostly in the visible range, with a major peak in the blue (400–450 nm), also known as the Soret band. It was therefore decided to use blue light in this study to test protection afforded by sunscreens because blue light is the major contributor to visible-light sensitivity after porphyrin precursor application and the noncoherent blue light device used in this study has a low irradiance (as opposed to a pulsed light source), which is ideal for phototesting. After topical application of ALA or MAL, patients are therefore exquisitely sensitive to visible light from the sun or intense ambient lighting. When the photosensitizer precursor is applied only on premalignant or malignant lesions to be treated, this photosensitivity is usually not a major problem and can even provide some additional therapeutic benefits, but physicians often apply ALA or MAL on broad areas or even on the entire face for the treatment of acne or photoaging or to prevent the appearance of new actinic keratoses.\textsuperscript{3–8} These off-label uses imply that it is imperative for patients to protect themselves from visible light in the first days after ALA or MAL application.

Current sunscreens are designed to protect against ultraviolet radiation. The SPF of a sunscreen relates to its ability to provide protection against ultraviolet B (UVB) rays. It has previously been shown that SPF is a poor predictor of UVA protection afforded by sunscreens.\textsuperscript{16} SPF is probably even less useful to assess the ability of sunscreens to protect against visible-light sensitivity. Organic sunscrening agents absorb mostly in the UVB range, with some agents, such as benzophenones, Parsol 1789, Tinosorb S and M, and Mexoryl SX and XL, providing protection in the UVA range,\textsuperscript{17} but these agents do not absorb in the visible range. Inorganic sunscreen agents such as titanium dioxide and zinc oxide can protect against visible radiation, but most commercially available inorganic sunscreens contain micronized particles of inorganic sunscrening agents. The UV spectral protection provided by these micronized particles is directly related to their size, with small particles (40 nm) providing protection mostly against UVB and larger particles (100 nm) providing UVB and UVA protection.\textsuperscript{18,19} With particles larger than 200 nm, it is possible to provide good visible-light protection, although this requires that the sunscreen appear white on the skin.\textsuperscript{18,19} Because this is less cosmetically acceptable, most inorganic sunscreens do not contain particles of that size.

Previous in vitro and in vivo studies on patients with diseases such as porphyria and chronic actinic dermatitis have suggested that sunscreens containing titanium dioxide can offer some protection in the visible range.\textsuperscript{20,21} Results from a study comparing sensitivity to visible light after application of ALA suggested that titanium-based sunscreens were superior to organic sunscreens,\textsuperscript{22} but this study used 12.7 mg/cm\textsuperscript{2} of sunscreen (compared with 2 mg/cm\textsuperscript{2} in the current study), which is significantly more than what is used in clinical settings. In addition, irradiation was performed with only one fluence, and a control area was not studied, which precluded the determination of a protection factor.

The current study showed that the very-high-protection tinted compact (Sunscreen B) had excellent ability to protect against blue light sensitivity induced by topical application of ALA. Despite having identical SPF and identical particle size and offering excellent UVA-UVB protection, Sunscreen A did not provide the same blue light protection. This was probably related to the higher iron oxide concentration present in Sunscreen B (3.2%) than in Sunscreen A (0.2%). This higher iron oxide concentration is responsible for the tint of Sunscreen B. An in vitro spectroscopic study evaluating various inorganic sunscrening agents showed that iron oxide was superior to zinc oxide and titanium dioxide in reducing transmission of visible light.\textsuperscript{23} It is also possible that the higher titanium dioxide and
zinc oxide concentration in Sunscreen B provided additional protection against blue light. An important finding of the current study was that all high-SPF sunscreens containing inorganic sun-screening agents do not offer identical blue light protection. It is probably not sufficient to ask patients to apply any high-SPF inorganic sunscreen after PDT. Even if patients use a high-SPF inorganic sunscreen that affords excellent UVA and UVB protection for outdoor activities, it might not afford sufficient protection against visible-light sensitivity.

When this study was initially designed, it was thought that exposure 3 hours after ALA application would assess the ability of the 2 sunscreens to protect against blue light sensitivity, as well as provide a blue light protection factor. Exposure 3 hours after ALA application showed that both sunscreens provided protection, although the protection provided by Sunscreen A was at the limit of statistical significance. However, the time between ALA application and blue light exposure was too short to be able to measure erythema in 9 of 10 subjects on the skin protected with Sunscreen B. In the only subject who presented some erythema, this was observed at 4 J/cm² and not at higher fluence, suggesting that a factor other than blue light exposure caused this erythema or that a technical problem occurred during exposure. After analysis of results from exposure performed 3 hours after ALA application, it was decided to amend the protocol to expose 10 more subjects 18 hours after ALA application, which is at approximately the peak porphyrin presence in the skin after ALA application and therefore the time when patient’s skin is most sensitive to blue light exposure. The exposure time 18 hours after ALA application and the addition of a 32-J/cm² fluence was performed to enable the detection of erythema with Sunscreen B to more precisely assess the blue light protection factor. All subjects presented erythema on the skin protected with Sunscreen B when exposure was performed 18 hours after ALA application, which enabled the precise calculation of a blue light protection factor. The blue light protection factor was 2 for the skin protected with Sunscreen A, compared with 21 for skin protected with Sunscreen B. These results show that SPF or the mere presence or absence of inorganic sun-screening agents is not enough to evaluate visible-light protection afforded by sunscreens.

This study was designed to assess protection against blue light in subjects receiving a topical photosensitizer precursor of porphyrins, although blue light sensitivity can also occur in other settings. For example, there are other porphyrin-based or porphyrin-derived photosensitizers, such as verteporfin and porfimer sodium, that are administered systemically.24,25 These photosensitizers also induce visible-light sensitivity that can, in the case of porfimer sodium, persist for many months.26 The different porphyrias also involve visible-light sensitivity. Visible-light exposure can trigger some of the idiopathic photodermatoses, such as polymorphous light eruption and especially solar urticaria, in some patients.27 It is possible that protection afforded by Sunscreen B can also be beneficial to these patients. This remains to be tested in a clinical setting.

We have started to use very-high-protection tinted compact in our clinical practice and are currently applying the sunscreen immediately after PDT, before patients leave the clinic. Patients who have undergone ALA PDT in the past have mentioned that they feel less pruritus and burning sensation when they walk outside for a few minutes than after previous PDT sessions, when they did not use sunscreen or were using a different type of sunscreen. Although our study showed significant protection, it did not show complete protection. All subjects presented erythema after blue light exposure. Therefore, patients using that type of sunscreen after PDT must also be reminded that it does not afford complete protection and that they still need to avoid sunlight and intense visible light.

In conclusion, this study showed that SPF cannot be used as an indicator of blue light protection. It also suggests that not all inorganic sunscreens are equal in providing protection against blue light and that...
sunscreens containing iron oxide may be superior. Further comparative trials would be helpful in assessing the protection afforded by different types of inorganic sunscreens. In addition, further trials should assess protection from sunlight afforded by sunscreens when sunscreens are used on the face in a clinical setting after PDT is performed with patients.

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References


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COMMENTARY: SUNSCREEN USE IN PHOTODYNAMIC THERAPY PROTOCOLS

The manuscript entitled “Protection afforded by sunscreens containing inorganic sunscreens against blue light sensitivity induced by aminolevulinic acid” by Robert Bissonette and colleagues is a valuable contribution to the field of photodynamic therapy (PDT) because it makes the first attempt to analyze the use of sunscreens in mitigating the photodynamic response. PDT has been in existence for more than a century, although its significant side effect profile has hampered its use.1 In the early part of the century, systemic photosensitizers were combined with broad-band light sources for the treatment of cutaneous tumors. Systemic PDT was plagued with the side effect of prolonged generalized photosensitivity after treatment, which persisted for weeks following treatment.1 In the early 1990s, the advent of the topical photosensitizer, 5-aminolevulinic acid solution, revolutionized the field by allowing for targeted therapy to individual cutaneous lesions.2 This approach limited the post-operative photosensitivity to the treated areas, which shielding the treated sites from light exposure would further mitigate. Inadvertent bright light exposure after PDT increases the risk of the phototoxic reaction, manifested by vesiculation, blistering, and crusting of treated areas.2 When topical ALA is combined with broad-band light sources such as blue or red light, the postoperative photosensitivity may last for several weeks, and phototoxicity may occur, particularly in the summer.1 The introduction of newer light sources in the past decade in conjunction with topical ALA application, including pulsed light and pulsed dye laser, have further minimized postoperative photosensitivity of the treated areas, diminished the duration of photosensitivity to several days, and greatly decreased the incidence of phototoxicity.3,4 Nevertheless, physical barriers to light exposure, such as broad-brimmed hats and avoidance of bright light, are necessary steps in current PDT protocols in order to avoid potential phototoxic complications.

In the current study, the application of two topical sunscreens was evaluated for its ability to block or diminish the PDT reaction, which is manifested primarily by erythema, when ALA application was followed by blue light exposure 3 or 18 hours later. These experiments tested two sunscreens, one containing 11% titanium dioxide and 2.4% zinc oxide and the other containing 15% titanium dioxide, 6.8% zinc oxide, and 3.2% iron oxide. It is important to stress that the sunscreens were applied after topical ALA application but before the blue light irradiation, thus evaluating protection from photoinactivation of photosensitizer, as opposed to postprocedural photosensitivity. Although this study design has one drawback in that the use of sunscreens postoperatively to mitigate photosensitivity from PDT was not directly evaluated, the findings presented by the authors are nonetheless an important first step toward this potential modification of PDT protocols. Their findings demonstrated that the second sunscreen, containing iron oxides and higher percentages of titanium dioxide and zinc oxide was the most effective at blocking the PDT response at 3 hours and that the mean phototoxic dose, the lowest dose of light required to induce erythema, was much higher for this sunscreen than for the unprotected control or the alternative sunscreen. These findings are intriguing because they suggest that the addition of iron oxides may be most effective at blocking the PDT response and potentially be useful in preventing phototoxic reactions. Iron oxides should be tested against titanium dioxide and zinc oxide to directly compare the efficacy of the different inorganic sunblocks.

Future research to follow up on these experiments would be helpful in directly assessing these sunscreens, particularly iron oxides, in their efficacy in mitigating post-PDT photosensitivity, as well as their effect on therapeutic efficacy. This would entail the application of ALA followed by irradiation with blue light or alternative light sources currently in use followed by application of sunscreen. The treated experimental sites would then be exposed to light of the appropriate wavelengths, mimicking sun exposure or indoor
lighting to assess the effect on postprocedure photosensitivity. The controls would include topical ALA alone with and without sunscreen, blue light alone without ALA, and ALA followed by photoactivation with and without sunscreen. Given the findings presented by Bissonette et al., the addition of post-PDT sunscreens, iron oxides in particular, may greatly decrease the risk of photosensitivity or phototoxicity, potentially eliminating the need for sun avoidance. It will be important to observe whether the use of sunscreens alter the efficacy of PDT in treating various conditions, because there may be a small contribution to PDT efficacy by ongoing activation of photosensitizer by sun or indoor light exposure after the light irradiation step. Published reports suggesting that two-step photoactivation, wherein a photosensitizer is activated by light illumination steps several hours apart, support the hypothesis that ongoing photoactivation may enhance efficacy. If ambient light further activates photosensitizers and may enhance therapeutic efficacy, the use of sunscreens after PDT, although making the procedure more tolerable, may do so at the expense of efficacy. The current deterrents to the use of PDT in risk–benefit analyses with patients who suffer from actinic keratoses, photoaging, or acne are the need for 2 days of sun avoidance, the wearing of sun-protective clothing, and postprocedural erythema. The application of highly effective sunscreens may serve as an important improvement in PDT protocols, potentially transforming PDT into a “no down-time” procedure and further enhancing its use in the routine treatment of actinic keratosis, photoaging, and acne, although its effect on therapeutic efficacy needs to be analyzed.

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References