Clinical Management of the Acute Sunburn Reaction

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Critical reviews of published human studies about pharmacologic agents used to treat the sunburn reaction show that systemic and topical corticosteroids have little or no clinically important effect on the sunburn reaction. Systemic and topical nonsteroidal anti-inflammatory drugs, when used at dosages to achieve optimal serum levels for anti-inflammatory effect, only result in an early and mild reduction of ultraviolet B-induced erythema. Due to the lack of demonstrated clinical efficacy of these and other medicines to eliminate sunburn or decrease healing time, we currently suggest conservative local symptomatic treatment with adequate pain control until the sunburn naturally resolves.

Sunburn is a clinical response to acute cutaneous solar photodamage due to excessive ultraviolet (UV) light exposure, and ranges from mild, painless cutaneous erythema to painful erythematous skin with associated edema and blistering. The primary pharmaceutical prevention of sunburn currently rests mainly with topical sunscreens, an area of study that lies beyond the scope of this review,[1] although recently systemic approaches to primary sunburn prevention have shown some promise. Large doses of vitamins A and E taken together for 8 days were reported to provide slight protection (sun protection factor [SPF] of 1.4) against the sunburn reaction induced by light bulbs.[2] Ingestion of fish oil for 3 months also has been found to significantly increase the mean minimal erythema dose (MED) over baseline.[3]

This article will mainly focus on medicines that have a theoretical potential to treat the sunburn reaction by blocking the natural progression of the biologic injury response. There are numerous reports in the literature that address this question, although few are well-controlled, double-blind studies. Medical management of the acute sunburn reaction, if effective, has the potential benefit of decreasing patient morbidity. Medicines with the ability to undo the carcinogenic effects of sunburn have the theoretical potential to mitigate the incidence of later skin cancer.[4] Various agents have been used experimentally in animals to block the later development of UVB-induced skin cancers, including vitamin E,[5] retinoids,[6] and alpha-difluoromethylornithine.[7] However, currently available medicines used to manage sunburn appear to have limited efficacy in blocking the progression of acute sunburns and an unknown impact on the skin cancer epidemic. For the purpose of this presentation, acute photosensitivity reactions due to endogenous or exogenous photosensitizers have been excluded.

Sunburn Reaction: Rationale for Therapy

The principal cause of sunburn in human skin is UV irradiation wavelengths of 290 to 320 nm, or UVB. Erythema begins to develop at approximately 3 to 5 hours after UVB exposure, reaches a maximum at 12 to 24 hours, and fades over 72 hours. While all of the specific mechanisms responsible for the erythema are unknown, absorption of UVB by DNA has been identified as the most likely event to initiate the reaction.[8] This is followed by a series of biochemical and immunologic events that cause inflammation. Histologically, one observes dyskeratotic and vacuolated keratinocytes known as sunburn cells, mild epidermal spongiosis, depletion of Langerhans cells, dermal edema, endothelial cell enlargement, and later a neutrophilic dermal infiltrate. Some of the substances that are thought to be inflammatory mediators include prostaglandins, lipoxygenase products, cytokines (*eg*, tumor necrosis factor-alpha), adhesion molecules, reactive oxygen radicals, and mast cell-derived mediators, such as histamine, and substance P.[9-12] Local cutaneous blood flow is increased about twofold following injury with UV light,[13] which contributes

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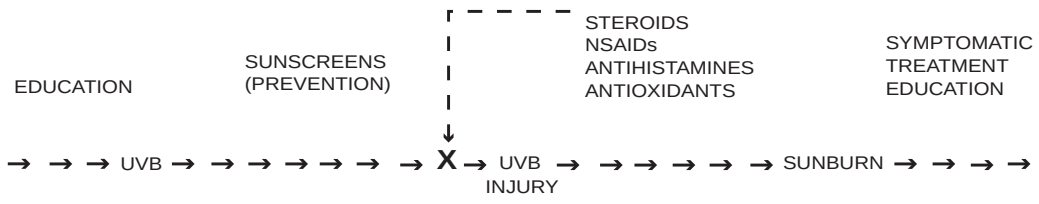
Figure 1

Pharmacologic Interventions in Sunburn



to sunburn-associated erythema. Therefore, in an attempt to decrease the production or diminish the effects of these mediators in the sunburn reaction, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), antioxidants, and antihistamines have been studied.

Criticisms of the Sunburn Research Model

Most of the studies about sunburn have been performed in laboratory settings where erythema is produced by exposure to UVB at a certain level of MEDs. This is a logical and controlled model of natural sunburn that focuses on the impact of a narrow spectrum of UV light, although it does not completely replicate sunlight and other naturally encountered environmental factors. The effect of therapeutic agents has typically been evaluated when the drug has been administered before or immediately after UVB exposure. In the clinical setting, sunburn patients do not usually develop erythema and pain until 3 to 5 hours after sun exposure. It would be ideal for a therapeutic agent to be effective after erythema has already developed, because this is when clinical treatment is most likely to be initiated. However, it also logically follows that if a drug initiated before or immediately after UVB exposure is ineffective, then it is unlikely to be effective after sunburn becomes clinically manifest.

Systemic and Topical Corticosteroids

Case reports from the 1950s suggested that oral corticosteroids were effective in reducing erythema, tenderness, and edema associated with sunburn in patients who presented to the emergency room with moderate to severe sunburn. Patients were treated with oral triamcinolone over a 48-hour period with dosages equivalent to a prednisone dose of 20 mg initially, followed by 5 mg every 3 to 6 hours.[14,15] However, subsequent studies with intradermal steroid injections showed little effect on UVB-induced erythema. Snyder and Eaglstein[16] studied the effect of intradermal injections of 125 µg triamcinolone acetonide (TAC) on UVB-induced erythema. Injection of TAC from 0 to 18 hours after single-exposure UV radiation (2 MEDs) prevented erythema if injected before visible erythema was apparent, or decreased erythema if injected after visible erythema was apparent. Kaidbey and Kurban[17] performed a similar study in healthy volunteers with intradermal TAC injections immediately after 1 to 3 MEDs of UVB; they observed a transient reduction of erythema, which was only significant with 1 MED of UVB, but not at higher MEDs. Although one can find recommendations in the medical literature for the use of oral and topical corticosteroids to treat sunburn,[18-20] little scientific support exists for this practice. There is only one double-blind, placebo-controlled trial of systemic corticosteroids in sunburn. Greenwald *et al*[21] irradiated four separate 2-cm^2 areas on subjects' backs for 4 consecutive days. Ten minutes after UVB on day 3, each subject started placebo or 80 mg prednisone that was continued for 4 days. With this study design, erythema could be evaluated when the drug was started 48 hours after exposure, 24 hours after exposure, 10 minutes after exposure, and 24 hours before exposure. There was no significant difference between drug and placebo in terms of UVB-induced redness, edema, or tenderness, regardless of when the drug was initiated.

Topical steroids have also been studied in the treatment of natural sunburn, with minimal if any effect. Russo and Schneiderman[22] studied the use of the medium-potency topical steroid fluocinolone in subjects with mild to moderate sunburn, most without evidence of blisters. In a double-blind fashion, subjects applied topical fluocinolone cream to a sunburned part of the body and an inert vehicle base to a symmetric, similarly exposed area, twice daily for 5 days. The majority of subjects initiated therapy on the day of sun exposure. The subjects reported no significant difference between treated sites, and had resolution of sunburn symptoms within 3 to 5 days. Snyder and Eaglstein[23] studied high-potency topical steroid fluocinonide 0.05% cream when applied after exposure to 3 or more MEDs of UVB. When applied 1.5 hours after erythema was first noted, there was

only faint blanching associated with fluocinonide, which was not significantly different from the control vehicle. Even when topical steroids were applied immediately before or after UVB, minimal or no suppression of erythema has been reported. Kaidbey and Kurban[17] applied a solution of the medium-potency steroid betamethasone valerate immediately after UVB, and found reduction of erythema only after 1 or 2 MEDs, but not at higher MEDs. Sukanto *et al*[24] studied three medium-potency topical steroid preparations, including betamethasone dipropionate lotion, when applied 24 hours before or after UVB exposure. All of the steroids showed some suppression of erythema, but only at MEDs of 2 or less.

Systemic and Topical NSAIDs

NSAIDs, such as aspirin (ASA), ibuprofen (IB), indomethacin (IM), and others, have been evaluated for the treatment and prevention of UVB-induced erythema. It has been observed that 100 mg IM administered orally decreases blood flow to skin injured by UV light by one-third,[13] which may account for part of its observed effect on sunburn. An early human study reported that single oral doses of ASA, IM, and fenoprofen were capable of delaying erythemic response after UV irradiation.[25] When utilized at sufficient anti-inflammatory doses, NSAIDs appear to be mildly effective, although almost all of the studies initiated NSAIDs immediately after UVB exposure and were most effective at approximately 6 hours after UVB, before peak intensity of erythema would be observed. They appear to be more effective than corticosteroids for suppression of early UVB-associated erythema.

In a double-blind crossover study, ASA in a dose of 1.2 g every 3 hours for three doses, initiated 30 minutes before UVB, showed a greater reduction of erythema than placebo at 4 and 6 hours post-UVB.[26] These effects were apparent at UVB doses as high as 4 and 6 MEDs. Snyder and Eaglstein[16] studied the effect of intradermal injections of IM and ASA on UVB-induced erythema. When injected from 0 to 18 hours after irradiation, both agents prevented erythema if injected before visible erythema, or decreased erythema if injected after visible erythema was apparent. IM was 45 times more potent than ASA. When the effectiveness of IM was compared at 3 and 18 hours post-irradiation, erythema was decreased to a greater extent and for a longer duration with injection 3 hours post-UVB. Morrison *et al*[27] reported that whereas IM delivered topically or intradermally decreased cutaneous erythema after exposure to UVB, 150 mg oral IM started 1 hour prior to UVB exposure and continued for 2 days was ineffective in limiting UVB-associated erythema in five of six subjects. Black *et al*[28] studied the effect of oral or topical IM on UVB-induced erythema (3 MEDs). Oral IM administered for the preceding 48 hours, or topical IM applied just after UVB exposure, both reduced erythema from a moderate to a mild level when evaluated 24 hours after UVB. Edwards *et al*[29] evaluated the effects of oral NSAIDs on UVB-induced erythema when initiated just prior to UVB and continued every 4 hours for a total of four doses. The dosages and timing of the drugs were selected according to those needed to achieve therapeutic anti-inflammatory serum levels (*eg*, 1,200 mg aspirin was given every 4 hours for a total of 3,600 mg). At 24 hours post-UVB, the increase in the mean MED (compared with pretreatment MED) was approximately 250% for all three treatments. This would be equivalent to an SPF of 2.5. Stern and Dodson[30] studied oral IB in the treatment of UVB-induced inflammation in psoriasis patients receiving UVB phototherapy. In this randomized, double-blind, crossover study, patients received 400 mg IB or placebo every 4 hours while awake beginning at the time of UVB exposure. Of the six endpoints (patient-observed erythema, technician-observed erythema, pruritus, skin pain, general discomfort, and nocturnal restlessness) assessed, only technician-observed erythema was significantly reduced with IB treatment. When the higher-dose UVB treatments were analyzed separately, there was a small yet statistically significant reduction in four of six endpoints associated with IB treatment.

Topical IM 2.5% solution has been suspected of having sunblock properties with an estimated SPF of 4,[3,31] a property that potentially may confound studies where topical NSAIDs are applied to the skin prior to administration of erythrogenic UV light. Snyder[32] studied the effect of topical 2.5% IM on UVB-induced erythema. There was a similar delay and reduction of erythema and warmth when IM was applied once immediately post-UVB or repeatedly every 2 hours for 48 hours post-UVB. Topical IM displays dose-dependent suppression of erythema up to 36 hours after UVB injury, with maximum effectiveness at 100 $\mu g/cm^2$.[33] Topical flurbiprofen has been shown to cause significantly greater blanching of UVB-associated erythema than topical IM after 4 hours,[34] and it also exhibits a concentration-dependent blanching on UVB-induced erythema that peaks with a 3% solution.[35] When compared with topical diflumidone, however, topical IM-treated skin exhibited significantly less UVB-associated erythema after 24 hours.[36] Kaidbey and Kurban[17] also studied the effects of topical IM on UVB-induced erythema. Topical IM was studied at concentrations ranging from 0.1 to 2.5% and applied immediately after 3 or 6 MEDs of UVB. There was a dose-dependent delay and reduction in erythema that was more pronounced at 6 hours com-

pared with 24 hours. IM was found to be much more potent in its effects than corticosteroids. However, neither of the agents reduced epidermal or dermal changes seen on skin biopsy 24 hours after UVB. Lim *et al*[37] studied the effect of topical IM 2.5% solution in two healthy volunteers, applied 20 minutes prior to 1 to 2.44 MEDs of UVB. With topical IM, the MEDs in both subjects increased from 25 to 39 mJ/cm^2, which is equivalent to an SPF of 1.6.

Combined NSAIDs and Corticosteroids

Although immediate UVB injury treatment with 5% suprofen cream and 0.1% triamcinolone acetonide cream was significantly more effective than either agent alone, therapeutic action was limited to the first 30 hours following UVB injury.[38] The authors of this research concluded that such combinations were not practical for clinical sunburn management due to these limitations.[38] A research group from Upjohn Research Clinics (Kalamazoo, MI) more recently reported that oral NSAIDs started prior to UVB exposure, together with post-exposure application of topical betamethasone dipropionate, reduced early post-UVB skin blood flow more than NSAIDs or topical corticosteroid alone.[39]

Antihistamines

There has been little formal study about the effect of antihistamines on sunburn. Edwards and Edwards[40] studied the effect of various antihistamines administered intradermally 15 minutes prior to UVB or at 2 and 4 hours post-UVB. There was no significant effect on erythema compared with controls regardless of the timing of injection. Farr *et al*[41] evaluated the effect of terfenadine on UVB- and UVC-induced erythema as measured by a reflectance instrument. Even when terfenadine was administered for 2 days prior to UVB and continued for 24 hours after UVB, there was no significant effect on erythema. The effectiveness of topical antihistamines in the treatment of sunburn is unknown. However, the use of topical diphenhydramine has been discouraged due to the risk for allergic contact dermatitis.

Antioxidants and Other Agents

There has been little evaluation of antioxidants for the treatment of sunburn. Werninghaus *et al*[42] compared oral vitamin E with placebo for photoprotective effect when administered for 6 months prior to UVB, finding no difference in the MED between the treatment and control groups. Thus, it appears unlikely that vitamin E alone would have efficacy for treating the sunburn reaction. We are unaware of clinical studies employing vitamins C, A, or fish oil to treat sunburn.

Topical Therapy and Analgesics

Various topical treatments have been recommended for symptomatic treatment of sunburn, such as emollients, cool compresses, and topical anesthetics. Topical anesthetics containing benzocaine carry a risk for allergic contact dermatitis, and should probably be avoided. Oral analgesics such as acetaminophen may be helpful for pain associated with sunburn.

Antibiotics

In our experience, infection as a secondary event complicating sunburn is very unusual. However, with epidermal injury and loss, there is a portal for pathogenic bacteria to enter, and when infection is suspected, appropriate microbiologic tests should be obtained and antibiotics started. Infections in the setting of sunburn may be clinically difficult to diagnose because typical sunburn is also associated with the classic clinical findings usually associated with infection, such as erythema, pain, warmth, blistering, erosions, and dermal edema.

Educational Opportunity and Skin Cancer Screening

Patients presenting to a health care provider for the care of an acute sunburn reaction provide an educational opportunity to teach primary prevention strategies in an attempt to prevent future sunburns. The increased risk of sunburn patients for synchronous and future skin cancer merits special consideration. A family history of skin cancer should be sought. Patient education should focus on the interventions currently available to decrease morbidity and mortality from skin cancer. Patients with sunburn should be given the opportunity to have their skin examined for skin cancer during the current visit or to schedule such a visit once the acute sunburn symptoms have resolved. Secondary prevention strategies for skin cancer, such as how to recognize skin cancer and how to perform monthly skin self examinations, should also be accomplished. The advantages of periodic professional follow-up for skin cancer surveillance should also be discussed.

Conclusion

Treatments that have the theoretical potential to alter the sunburn reaction, such as corticosteroids and NSAIDs, have not been shown to have a clinically important impact. Certainly, the criteria of efficacy and safety suggested in 1975 by Eaglstein[43] for evaluating therapeutic agents in sunburn management have not been convincingly demonstrated. Although NSAIDs appear to have a slightly greater effect than corticosteroids when used at optimal anti-inflammatory dosage, almost all of the studies initiated ther-

apy immediately after or before UVB exposure, which does not replicate the clinical situation in which these agents would be used. Our conclusion about the ineffectiveness of NSAIDs for sunburn treatment is also supported by Lichtenstein *et al*[44] in a previous comprehensive review about the use of NSAIDs for dermatologic conditions. In addition, the adverse effects that patients may experience with these agents should be considered, especially with the oral administration of high doses of NSAIDs for a self-limited condition.[45] Combination therapy with topical corticosteroids and NSAIDs also does not appear to have clinical usefulness for patients presenting with symptomatic sunburn due to the pre-erythema administration schedules employed for NSAIDs and steroid preparations in clinical studies, and a clinical effect that is limited to the earliest phase of the cutaneous UV injury response.

The most rational management for sunburn, based on current evidence, is symptomatic treatment with bland emollients and cool compresses along with adequate pain control. An oral NSAID is likely to be no more effective for analgesic therapy in sunburn than acetaminophen. However, even common nonprescription pain medicines such as acetaminophen should be used with caution. It has recently become recognized that acetaminophen may cause acute liver failure and death, even within the recommended dose range of 4 g/24 hours or less in association with excessive alcohol use, fasting, and genetic differences.[46] Restricting acetaminophen intake to 2 g daily may be safer.[47] In addition, patients receiving warfarin anticoagulation therapy may experience dangerous International Normalized Ratio elevations if more than 9,100 mg/week of acetaminophen is taken.[48]

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