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UVA-1 phototherapy

Speaker: Dr. G. A. Elmets

Since Krutmann first demonstrated the effectiveness of ultraviolet A-1 (UVA-1) therapy in the treatment of atopic dermatitis in 1992, a number of skin diseases had been successfully treated with UVA-1 of various doses.

UVA-1 (340-400 nm) has unique photobiologic properties. It is less erythematogenic and carcinogenic. It penetrates deeper into the dermis. It targets various cell types (T cells and mast cells) and can generate reactive oxygen species. The mechanism of action of UVA-1 can be summarised as follows:

1. It reduces the survival of transformed T and B lymphocytes by mediating singlet-oxygen damage triggering immediate apoptosis.
2. It inhibits the expression of the intracellular adhesion molecules-1.
3. It enhances the expression of the anti-inflammatory keratinocyte-derived cytokine IL-10.
4. It reduces the number and functional activity of dendritic cells in the dermis bearing the human high-affinity receptor for IgE (FC ε RI).

The spectrum of skin diseases treated with UVA-1 included atopic dermatitis, dyshidrotic eczema, mycosis fungoides, systemic sclerosis and urticaria pigmentosa.

In 1992, Krutmann studied the therapeutic effectiveness of high-dose UVA-1 irradiation in the management of patients with acute exacerbation of atopic dermatitis. He found that high-dose UVA-1 induced a significant clinical improvement and reduced the elevated serum level of eosinophil cationic protein in patients with atopic eczema. Petering later compared the effects of localised high-dose UVA-1 irradiation versus topical cream PUVA for chronic dyshydrotic palmo-plantar eczema. Twenty-four of the 27 patients showed a good response to both arms of treatment as measured by the Dyshidrotic Area and Severity Index scores. The UVA-1, however, did not require the application of topical 8-methoxypsoralen cream which might cause phototoxic reaction. Also it was more convenient to deliver UVA-1 therapy as compared with the topical cream PUVA. In 2001, Zane used UVA-1 to treat patients with widespread plaque-type, nodular and erythrodermic mycosis fungoides. The patients received an average of 21.9 treatments with a mean cumulative dose of 2148.5 J/cm^2. Out of the 13 treated patients, 11 patients had a complete remission while the remaining two had partial remission. The control lesions that did not receive irradiation had no response, suggesting that the phototherapy did not work by a systemic mechanism. Side effect was mild. Only one patient complained of burning of skin and seven patients had mild skin dryness. In 2003, Gobello reported

his use of UVA-1 in treating patients with urticaria pigmentosa. The patients were divided into two groups, each of 10 and 12 patients, and treated with high-dose (130 J/cm^2) or medium-dose (60 J/cm^2) respectively. UVA-1 phototherapy was administered five times per week for two weeks. The authors found that both clinical signs and symptoms (presence of Darier's sign, number of skin lesions, intensity of pruritus, quality of life measures) and histology (number of dermal mast cells) improved considerably by the end of treatment. This was maintained during the six-month follow up. Lastly, Mortia had tried medium-dose UVA-1 on patients with systemic sclerosis, an intriguing fibrosing disease with unclear pathophysiology. In this study, four patients with systemic sclerosis received nine to 29 treatment of UVA-1 at 60 J/cm^2. All patients had clinical improvement as evidenced by an increase in joint passive range of motion, skin temperature, cutaneous elasticity. Histologic evaluation of the skin specimen obtained before and after UVA-1 phototherapy revealed loosening of collagen bundles and the appearance of small collagen fibers. The finding was supported by recent studies indicating that UVA-1 could induce apoptosis of skin-infiltrating T cells and the expression of matrixmetalloproteinase-1 in human dermal fibroblasts. There are potential uses of this new modality in treating HIV patients with psoriasis, keloid, hypertrophic scar, graft versus host diseases and lichen sclerosis et atrophicus. However, the benefit needs to be weighed against the side effects. The acute side effect of UVA-1 includes activation of viral infection, aggravation of UVA sensitive photodermatoses and transient post inflammatory hyperpigmentation. On a long-term basis, photoaging and photocarcinogencity are of primary concern.

Learning points:

Phototherapy with UVA-1 is a promising treatment modality for a variety of difficult skin diseases. Despite its initial success, the optimal dosing schedule and the long-term side effects need further study.

Mechanisms of Photoaging: New Insights

Speaker: Dr. D.H. McDaniel

Aging skins are dry, scaly, wrinkled with telangiectasia and pigmentary changes. Under histology section, there is an increase of glycosaminoglycans and elastosis; disorganised collagen fibres; decreased number of Langerhans cells; irregular size and shape of keratinocytes and melanocytes. The biochemical changes detected in aging skin included an increase of free radicals and matrix metalloproteinases, in addition to the DNA and immune system damage.

Factors affecting aging can be intrinsic such as the genetic inheritance or environmental. The latter consists of ultraviolet light exposure, smoking, stress, sleep deprivation or concomitant diseases.

Photoaging results from excess exposure to UV light. Both UVA and UVB have role to play but the exact mechanism is unclear.

Recently there is increasing understanding about the role of UV induced reactive oxygen species (ROS) in causing some of the changes observed in photoaging. ROS are the free radicals and reactive oxygen molecules (singlet oxygen, hydrogen peroxide) that are present in excess when cells are under increased oxidative stress such as high metabolic demands, sunlight, smoking and pollutions. Under normal circumstances, these ROS are kept to a minimum by cellular enzymes and controlled metabolic processes. In case of excess, they may enhance the process of photoaging. Two possible pathways have been postulated. Firstly, these ROS may induce the transcription factor AP-1 (activation protein-1) causing an increase of matrix metalloproteinases and leading to the breakdown of collagen. On the other hand, ROS may activate the NF-κB (Nuclear factor κB) causing the release of cytokines and resulting an increase of the inflammation response. In addition, ROS can modify proteins in tissue to form carbonyl derivatives and altered

membrane fluidity by peroxidation of the lipid in membranes. What causes hyperpigmentation in photoaging skin is unclear. However, increased endothelin-1 activity in keratinocytes, and increased endothelin-B receptor and tyrosinase in solar lentigines have been demonstrated. Also melanogenesis can be stimulated by DNA damage.

Based on our understanding of the photoaging process, various strategies have been tried to minimise these damages.

1. Sunscreen: despite its success in experimental setting, it is dangerous to equate this with clinical protection. Firstly, the actual amount (0.5 mg/cm^2) of sunscreen applied usually is much lower than those tested (2 mg/cm^2). Secondly, there is no 'perfect' sunscreen that covers the whole spectrum of UV light. Thirdly, important biologic events such as DNA damage continue at suberythemal levels of irradiation.
2. Topical anti-oxidant: an attractive treatment aiming to reduce photodamage, yet, certain obstacles need to be overcome. Compounds need to be chemically stable and cosmetically acceptable. The formulation needs to contain high concentration of the antioxidant in order to allow adequate dermal concentration. Vitamin C and Vitamin E are natural antioxidant and are candidates for topical formulation.
3. Tazarotene: recent study had shown that tazarotene 0.1% cream applied once daily can result in clinically and statistically significant improvement in multiple signs of photodamage (i.e. fine wrinkling, mottled hyperpigmentation, lentigines, elastosis, etc). The exact mechanism of how tazarotene improves photodamaged skin is far from clear. Its induction of transforming growth factor β, which activates the fibroblasts to increase collagen synthesis, may explain its effect on wrinkle improvement.

Learning points:

A better understanding of the patho-physiology of photoaging will improve our ability to prevent or even reverse the process of photodamage.