Novel Topical Therapies in Cosmetic Dermatology

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Novel topical therapies in dermatology represent the cooperative efforts of the cosmetic chemist, who researches new biologically active agents, and the dermatologist, who verifies the safety and efficacy of the active agents. Currently, over-the-counter products are available that alter the structure and function of the skin in ways that are important to the dermatologist. These alterations can be improvements in skin functioning or a reversal of the cutaneous aging process. Novel products that fall into this category include skin lightening agents, vitamins, enzymes, and anti-inflammatory agents.

Skin Lightening Preparations

Skin lightening preparations prevent and improve post-inflammatory hyperpigmentation by decreasing the production of melanin. The most common prescription active agent used in the United States for this purpose is hydroquinone in concentrations varying between 3% and 5%. Its apparent concentration can be increased by combining hydroquinone with glycolic acid or tretinoin to exfoliate the stratum corneum and increase penetration.[1,2]

The safety of hydroquinone in certain formulations has been questioned, however. Its use has been banned in Japan and severely restricted in South Africa. This is because of concern regarding its long-term safety with uncontrolled use and the recognition that it can contribute to the development of irreversible exogenous pigmentation, known as ochronosis.[3] Problems with hydroquinone lightening creams outside the United States have been mainly because of the unsupervised use of over-the-counter high concentration products.

Hydroquinone functions to decrease melanocyte pigment production through degradation by auto-oxidation, tyrosinase, and phenol oxidases into highly reactive oxygen radicals, semiquinones, and quinones.[4] These reactive substances prevent melanin production. The reactivity of hydroquinone can be attested to by the fact that it can even oxidize in the tube or bottle. This has led to the search for new skin lightening preparations.

A novel chemical active, known as azelaic acid, shows great promise in lightening postinflammatory hyperpigmentation in both white and oriental skin.[5] It is a naturally occurring straight-chain, 9-carbon, saturated dicarboxylic acid that in vitro is a competitive inhibitor of tyrosinase and an inhibitor of DNA synthesis in the pigment-producing cell.[6] The effect of azelaic acid on pigmentation is also potentiated by topical tretinoin. Further research is currently ongoing to enhance the effectiveness of azelaic acid on melanocytes.

Topical Vitamins

Vitamins are currently a popular additive to a variety of skin-care products, including cleansers, moisturizers, barrier creams, and therapeutic formulations. They are a food and as such can be added to cosmetics without creating difficulties with the Food and Drug Administration. It is important to notice that most vitamin-containing topical products make no efficacy claims directly related to the effect of the vitamin on the skin.

Many topically applied vitamins are touted to prevent aging because of their role as antioxidants. Oxidation occurs because of the formation of oxygen radical species, such as hydrogen peroxide, superoxide anion, and hydroxy radicals, that transfer their energy to living cells, resulting in damage. Cellular proteins, enzymes, DNA, and RNA are damaged, but oxidative damage to the unsaturated fatty acid component of cell membranes is of primary importance. Hydroxy radicals initiate lipid peroxidation in cell membranes to form lipid peroxides that are responsible for accelerated cutaneous aging.[7]

Several currently popular topical vitamins function as antioxidants endogenously. These include vitamin C, vitamin E, vitamin A, ubiquinone, and lipoic acid. Other vitamins are added to topical moisturizers for their effect on skin barrier, such as panthenol and niacinamide. Each of these topical vitamin additives will be discussed individually.

Vitamin C

Vitamin C has captured the attention of the dermatologist in the form of topical liquid and lotion formulations that are available from physicians and from mass merchandisers. These products are designed to confer antiaging benefits because vitamin C, in the form of L-ascorbic acid, functions as an antioxidant by scavenging

and quenching free radicals and by regenerating vitamin E from its radical form.[8,9] It is well established that vitamin C is necessary for wound healing because it is a cofactor for lysyl and prolyl hydroxylase, which stabilize the triple helical structure of collagen. Whether oral or topical supplementation of vitamin C enhances wound healing is controversial.

The value of vitamin C supplementation is theoretically to maintain the body reservoir of 1500 mg of the vitamin, which is rapidly depleted when the body is exposed to UV light. Some researchers believe that natural dietary sources of vitamin C, such as vegetables and citrus fruits, are the best method of restoring body reserves, whereas others believe that the poorly ripened fruits now sold in grocery stores are vitamin C deficient. These researchers believe that synthetic vitamin supplementation is important; however, vitamin C can function as a oxidant in the presence of iron.

Even though much is available in the popular press regarding the merits of topical vitamin C, little has been published in the peer-reviewed dermatology literature. Some investigators have demonstrated enhanced cutaneous vitamin C levels after topical application of 10% L-ascorbic acid; however, this work was performed on a porcine model.[10] Other human studies have demonstrated a decrease in the minimal erythema dose and less erythema after UV-B exposure in subjects treated with topical 10% L-ascorbic acid, but the sample size was limited.[11] Vitamin C has also been purported to produce lightening of skin dyspigmentation in the form of magnesium L-ascorbyl-2-phosphate, but no well-controlled studies exist.[12] The challenge remains for researchers to embark on large-scale double-blinded placebo-controlled studies to demonstrate the value of topical vitamin C.

The major hurdle in developing topical vitamin C preparations, other than the proof-of-efficacy issue, is insuring stability. Vitamin C is inactivated on exposure to light, moisture, and oxygen. Figure 1 demonstrates a vitamin C liquid formulation that has oxidized in the bottle. Vitamin C preparations that turn brown no longer have any biologic value because their ability to function as an antioxidant is lost. Patients should be instructed to discard vitamin C products that have discolored.

Vitamin E

Vitamin E, like vitamin C, is a naturally occurring antioxidant within the body. Even though the concentration of vitamin E in the epidermis is extremely small at 1.0 nmol/g,[13] it is the most important lipid-soluble membrane-bound antioxidant in the body.[14] Vitamin E and vitamin C work synergistically because vitamin E can regenerate its antioxidant capabilities in the presence of vitamin C.[15] The form of vitamin E with the most biologic activity is alpha tocopherol, which functions to terminate lipid radical chain reactions. It stabilizes membranes against damage by phospholipase A, free fatty acids, and lysophospholipids.[16] Vitamin E may also protect membrane proteins containing selenium or sulfur.

The body stores of vitamin E are maintained through the intake of vegetables, oils, seeds, corn, soy, whole wheat flour, margarine, nuts, and some meats and dairy products.[17] Again, the value of topical application awaits further study. A review of the literature yielded articles reporting that alpha-tocopherol could inhibit UV-B–induced edema and erythema, conferring a skin protection factor of 3 after multiple applications.[18] This is thought to be because of alpha-tocopherol's ability to marginally absorb light and to function as a free-radical–quenching, lipid-soluble antioxidant.[19] However, oral vitamin E was shown to confer no photoprotective effects.[20]

Despite the lack of good dermatologic data to demonstrate the topical efficacy of vitamin E as an antioxidant, its ability to improve the aesthetic aspects of skin are well grounded in the cosmetic science literature. Skin benefits attributed to vitamin E include improved moisturization, increased softness, and better smoothness. In this usage, it is felt that vitamin E acts as a humectant, attracting water to the epidermis. Vitamin E is an active agent added to many moisturizers in the over-the-counter market.

Vitamin A

Vitamin A and its precursor beta-carotene are from a family of natural and synthetic-related derivatives collectively known as retinoids. Retinoids are biologic modifiers that produce receptor-specific effects within the body. The antiaging effects of synthetic retinoids, such as tretinoin, are well documented in the literature.[21]

Like vitamin C, the retinoids are difficult to formulate because of their inherent photoinstability. As antioxidants, they degrade immediately on light exposure to biologically inactive forms. For this reason, vitamin A oral supplements are packaged in amber bottles to prevent UV radiation exposure, and prescription retinoids are packaged in opaque metal or plastic tubes. Topical preparations in which the retinoid has oxidized turn yellow, an indication that some degradation has occurred.

Even though retinol palmitate is the easiest retinoid to

topically formulate in the over-the-counter market, it is not a biologically active form in the skin. Topical activity of retinol palmitate is thought to occur after cutaneous enzymatic cleavage of the ester bond and subsequent conversion of retinol to retinoic acid. It is this cutaneous conversion of retinol to retinoic acid that is responsible for the anti-aging claims made by some over-the-counter retinol formulations. Unfortunately, only extremely small amounts of retinol can be converted by the skin, but research continues to develop enhanced efficacy products.

Ubiquinone

Ubiquinone, also known as coenzyme Q10, is a fat soluble vitamin-like substance synthesized in all tissues of the body. It is not a true vitamin because it can be manufactured endogenously from tyrosine. It is the "ubiquitous" nature of this quinone family coenzyme that led Morton in 1957 to name the substance he isolated from rat liver as ubiquinone. Folker and coworkers at Merck defined its chemical structure, but the first human application for oral ubiquinone was developed by Yamamura to aid in the treatment of congestive heart failure. Ubiquinone is found in mitochondria as part of the electron transport chain and is felt to aid in heart muscle contractility.[22] Medications, such as lovastatin, used to lower cholesterol, are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and also block ubiquinone synthesis.[23] Ubiquinone supplementation orally is also used in Japan for patients with periodontal disease and cancer.

Ubiquinone may also function as an antioxidant by providing electrons to oxygen radicals. For this reason, it is becoming an additive in many therapeutic dermatologic moisturizers. Because it is an endogenous antioxidant synthesized by the body when a normal solid food diet is consumed, it is unclear how topical supplementation affects the skin. More data must be forthcoming before its dermatologic utility can be documented.

Lipoic Acid

Lipoic acid is another relatively new endogenous antioxidant to topical dermatologic preparations. Lipoic acid is both water and fat soluble and is manufactured by the body to aid in the use of glucose, the regeneration of vitamin C, and the increased synthesis of glutathione. Although no side effects have been documented from excessive intake of ubiquinone, oral ingestion of lipoic acid has been associated with overalertness, insomnia, and stomach upset.

When applied topically, lipoic acid has been claimed to function as an anti-inflammatory by inhibiting kinases, transcription factors, tumor necrosis factor-alpha, and collagenase. No controlled blinded trials with topical lipoic acid in the medical literature were found on extensive literature search. Again, it is hoped that more data are forthcoming on the topical utility of this antioxidant. Well-designed multi-investigator independent studies are a must when documenting the role of endogenous antioxidants on the skin surface.

Panthenol

Panthenol, also known as vitamin B5, is a common additive to hair shampoos and conditioners because of its ability to condition and beautify the hair. It has the ability to function as a humectant, increasing the water content of the hair. This improves hair elasticity because water is the plasticizing agent of the hair.

Water is also the plasticizing agent found in skin. For this reason, panthenol also has a role in enhancing skin moisturization to both attract and hold water. It is typically used in skin moisturizers in concentrations of 5%. New moisturizer formulations containing panthenol and other vitamin humectants are currently under development.

Niacinamide

Niacinamide is a relatively new ingredient to the skin care market. It does not produce the flushing associated with niacin and is extraordinarily stable to heat, light, and oxygen. Its water solubility also makes it easy to formulate as a therapeutic moisturizing ingredient.

A review of the dermatologic uses of niacinamide showed that a 4% niacinamide gel is of dermatologic benefit in the treatment of papular and pustular acne.[24] Other reports include its use in the treatment of bullous pemphigoid[25,26] and necrobiosis lipoidica.[27] Niacinamide also has been shown to promote antitumor characteristics in keratinocytes[28] and to suppress UV-B photocarcinogenesis.[29]

The beneficial cutaneous effects from the topical application of niacinamide, especially the improvement in photocarcinogenesis, have led to further research as to the usefulness of niacinamide as a moisturizer additive.

Summary of Topical Vitamins

The development of biologically active topical vitamin preparations has been hindered by formulation difficulties. Vitamins A and C are light sensitive and difficult to stabilize on the skin. Vitamin E is a fat-soluble vitamin that does not readily penetrate the skin. Therapeutic vita-

min preparations must disassociate from the vehicle, reach the target tissue in a biologically active form, and remain in the target tissue long enough and in sufficient concentration to deliver the desired antioxidant effect. Presently, only oral vitamin preparations can meet these criteria, yet the search continues for a vehicle that can effectively deliver vitamins to the skin topically.

Anti-Inflammatory Agents

One of the concerns regarding cutaneous irritation, either from surfactants or exfoliant treatment products, is the presence of chronic low-grade inflammation. It may be that chronic inflammation contributes as significantly to extrinsic aging as UV radiation. This has led to the search for topical anti-inflammatory agents suitable for long-term use, without the cutaneous side effects of topical corticosteroids. Experimental formulations of topical indomethacin are being investigated for their ability to inhibit long-term UV-A–induced skin sagging. Experimental sunscreen formulations incorporating indomethacin are one of the new frontiers in photoprotection. These topical anti-inflammatory agents are used in conjunction with pigments or particulates to provide broad-spectrum sun protection with a mechanism for reducing the effects of any oxygen radicals that might occur as the sunblock is physically removed from the skin.

Enzymes

Enzymes, used for years to enhance the stain-removing qualities of laundry detergents, are finding their way into topical cutaneous preparations. These proteolytic enzymes, such as papain and bromelain, are being used for their ability to dissolve desmosomes, thus encouraging stratum corneum sloughing.[30] They perform the same function on the stratum corneum as alpha hydroxy acids, without the need for a low pH. Because they thin the stratum corneum, they also enhance the penetration of topical agents.

The Future of Topical Agents: Improved Penetration Enhancers

The key to the development of new topical therapies is the ability to enhance the penetration of active agents through the stratum corneum. Any biologically active substance can become an effective therapy if it can reach the target tissue. Thus, the vehicle in which the active agent is formulated is the key to a successful formulation. This has opened up a whole new area of research into the realm of penetration-enhancing vehicles.

Some penetration enhancers are well known to the dermatologist, such as propylene glycol, which alters the barrier characteristics of the stratum corneum. Other agents, such as isopropyl myristate, are able to penetrate into the liposomal bilayers of cell membranes. Pyrrolidone derivatives interact with both keratin and the stratum corneum lipids to drive substances into the skin. Last, urea can split hydrogen bonds between the keratinocytes, allowing increased hydration of the skin.

Water is probably the most important penetration enhancer because skin can absorb 3 to 5 times its weight in water. This results in a 2-fold to 3-fold increase in the penetration of polar molecules. Simply by occluding the skin, penetration can be enhanced, a fact well known to the dermatologist. This is the basis for many of the "patches" that are sold for delivering topical agents. The occlusion of the plastic patch theoretically hydrates the skin and forces the therapeutic agent into the skin.

Penetration of topical agents can also be enhanced by considering active ingredient molecular size, degree of disassociation, pH, volatility, and solubility in lipids and water.[31] The physical characteristics of the vehicle and application technique also play important roles. Penetration is impacted by the viscosity of the formulation, the skin area of application, the frequency of application, and the degree of friction created by rubbing. Each of these variables offers new opportunities for research into topical dermatologic therapies.

The future of novel topical therapies in dermatology lies in enhancing vehicle delivery to targeted sites, providing enhanced efficacy with minimal side effects. Many biologically active substances are available with profound cutaneous effects; however, the skin is designed to prevent penetration indiscriminately. Overcoming this penetration barrier selectively is the challenge of the future. Once this is accomplished, new novel topical formulations containing vitamins, enzymes, and anti-inflammatory agents with improved efficacy will dominate cosmetic dermatology.

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