



Hydroxy Acids and Retinoids in Cosmetics

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The alpha-hydroxy acid family is composed of different compounds with wide application for the treatment of several dermatoses. One of their major indications is chemical peeling and their use in creams and/or lotions also improves the manifestations of cutaneous photoaging. Several factors influence the efficacy of these alpha-hydroxy acids and knowledge of them may prevent complications. Retinoids were introduced for photoaging and for the treatment of other dermatoses more than two decades ago and were an important advance in dermatological therapeutic resources. Risks and benefits of each treatment with these compounds should be properly assessed and monitored by the dermatologist.

Introduction

The use of drugs on the skin surface aims at the prevention of illnesses and has as its main purpose the protection and preservation of the normality of skin. Because in the last twenty years many patients have also become concerned with their appearance, dermatologists now have to deal with Cosmetics as well. This certainly arises in great part from the different information sources that exploit rejuvenation methods, including the use of vitamins A, C, and E, chemical peelings, drugs that revitalize collagen, filling substances for scars or expression marks, botulinum toxin and subcision, among others. The importance of vitamin A was discovered during World War I¹ and subsequent research showed that its deficiency gives rise to xerosis and follicular hyperkeratosis, changes that quite frequently occur in various dermatological conditions. The "retinoid project" was launched in 1968 to synthesize compounds similar to vitamin A by chemical manipulation of its molecule to improve clinical efficacy and

curtail side effects.² The use of these substances in therapy probably dates back some 3000 years to ancient Egypt, where liver was used to treat endemic night blindness.³ Retinoids' modern history, however, began in 1909 when Steps¹ discovered an essential factor for the viability of the embryo in the fatty extract of egg yolk, which he called vitamin A. The addition of the synthetic retinoids to the therapeutic armamentarium in the early 1980s marked a major advance in the treatment of certain skin diseases. Through the ages alpha-hydroxy acids have been used in a variety of cultures. In Egypt, Cleopatra bathed in sour milk, and during the French revolution the ladies of the court applied fermented wine to their faces.⁴ Recently, alpha-hydroxy acids have been incorporated into a variety of creams, lotions, and cleansers for general use. They are also being used in a variety of chemical peelings.

Skin Structure and Function

Skin functions include protection, heat regulation, immune response, biochemical synthesis, and sensory detection; it acts as a two-directional barrier to prevent water and electrolyte absorption and loss. The epidermis, the most superficial layer and, more specifically, the stratum corneum, plays the major role. The stratum corneum is formed by nonviable corneocytes, which are cells that have lost the nucleus and cytoplasm organelles. Fibrous proteins or keratin are aligned in intercrossed disulfidic macrofibers, along with filaggrin, the main protein component of the keratolytic granule. The cells develop a cornified involucre resulting from the intercrossing of involucrine and keratohyaline. This constitutes the insoluble exoskeleton that acts as a rigid structure for the internal keratin filaments. Lamellar lipids accumulate in the intercellular spaces, which are strongly hydrophobic. The combination of cornified hydrophilic cells in hydrophobic intercellular material is a barrier for hydrophilic and hydrophobic substances.⁵ With age, the skin's natural rejuvenation process slows drastically and the skin becomes thinner, drier, and less elastic. This aging process has intrinsic and extrinsic components.⁶⁻⁸ Intrinsic aging comprises the geneti-

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cally clinical, histological, and physiologic changes that occur in the skin throughout the body with the passage of time. Extrinsic aging is a cumulative degenerative process induced by decades of exposure to harmful environmental conditions, mainly solar ultraviolet radiation.⁶⁻⁹ Concurrent processes of intrinsic and extrinsic aging produce distinct skin changes, including development of fine and coarse wrinkles, leathery texture, mottled hyperpigmentation, and dryness. There is a marked loss of elasticity, and hyperkeratinization occurs, causing the corneocytes to adhere in excess, accounting for the thickening of the stratum corneum.^{6,8,9} In papillary dermis, photodamaged elastic fibers are short and fragmented, in contrast with the appearance of normal or nonphotodamaged elastic fibers, which are long, wavy, and nonfragmented.^{6,8,9} The greater understanding of the skin structure and function has allowed the development of efficient care products with appreciable beneficial effects,^{10,11} and both alpha-hydroxy acids and retinoids have a capacity of reducing cohesion between corneocytes and, consequently, decrease the width of the stratum corneum, especially in situations of hyperkeratosis.^{3,12}

Alpha-Hydroxy Acids

Alpha-hydroxy acids are a special group of nontoxic organic acids found in natural foods and are often commercially referred to as "fruit acids."^{4,13} They are weak organic acids and structurally all of them have one hydroxyl group attached to the alpha position of the acid (first carbon following the acid group). Although they are found in nature in sugarcane (glycolic acid), sour milk (lactic acid), and fruits (malic, citric and tartaric acids), the alpha-hydroxy acids used in dermatological and cosmetic products are usually produced synthetically.^{6,14}

Mechanism of Action

The exact mechanism of action of these acids is still unknown; however, it has been shown that at low concentrations alpha-hydroxy acids decrease corneocyte cohesion at the lower levels of the stratum corneum and it has been suggested that this occurs by interference with the formation of ionic bonds.¹³ Essentially, by dissolving adhesions between cells in the upper layers of the skin, alpha-hydroxy acids induce shedding of dry scales from the skin's surface, commonly referred to as exfoliation. In so doing, they stimulate the growth of new skin, resulting in a rejuvenated, fresher complexion.^{14,15} Analysis of experimental and clinical data has suggested theories for the mechanism of action of alpha-hydroxy acids topically applied to the skin. These acids reduce the calcium ion concentration in the epidermis and remove calcium ions from the cell adhesions by chelation. This causes a loss of calcium ions

from the cadherins of the desmosomes and from other types of junctions (adherens and tight junctions and also divalent metallic cation-dependent cell adhesions), resulting in a disruption of the adherence, which results in shedding/flaking.¹⁶ Another theory is that the protein chains are separated, that is, there are two chains linked by hydrogen bonds, and an alpha-hydroxy acid may adhere to them. Thus, at low concentrations, alpha-hydroxy acid forms a bond with the chains that are then slightly separated. At high concentrations the chains may be separated beyond a certain limit, causing desquamation.¹² A third theory involves ceramides linked to corneocytes. The natural moisturizing factor (NMF) in the stratum corneum is partially composed of lipids, including ceramides. Some of these are linked to the surface of the corneocytes by strong bonds. An ester bond could happen between a glutamic acid chain and the alcohol function of a carbon atom of the ceramide. Alpha-hydroxy acid may change the ester bonds or prevent their formation. Without the ceramide layer, the corneocytes can desquamate more easily.¹² The main cosmetic actions of these acids on the skin are increased exfoliation and moisturization.^{6,14} These and other proposed mechanisms of action have the following effects:

1. Increased exfoliation: low concentration of alpha-hydroxy acids facilitates shedding of the outer layer of the epidermis by interfering in intercellular ionic bonding, thereby reducing corneocyte cohesion at the lower level of the stratum corneum. Higher concentrations further reduce corneocyte cohesion and cause the thickened, hyperkeratotic stratum corneum to shed in sheetlike fragments, becoming thinner. Very high concentrations and low pH may cause epidermolysis.
2. Moisturization: helps diminish the appearance of fine lines and maintain the proper moisture level of the skin.
3. Increase of dermal thickness: in higher alpha-hydroxy acid concentrations both epidermal and dermal effects are observed.
4. Increase of dermal perfusion: alpha-hydroxy acids have definite vascular effects, as evidenced by erythema and vasodilatation that last for hours to days following treatment.⁶

Factors Influencing the Efficacy of Alpha-Hydroxy Acid Products

Several factors influence the effects on the skin, such as acid concentration, product pH, amount of free acid present, acid type, vehicle used, duration of exposure, and patient's skin type.⁶

Concentration

Higher concentrated alpha-hydroxy acid products generally deliver better results. Some studies have shown that higher concentrations increase epidermal and dermal firmness and thickness, clinical improvement in skin smoothness, and also the aspect of lines and wrinkles.^{6,10,15}

pH

Although pH and concentration are both relevant for determining the safety and efficacy of alpha-hydroxy acids, there is increasing evidence that pH is a more important factor than concentration. The lower the pH, the greater the potential for skin irritation. The higher the pH, the more the irritation drops off.^{6,10,15} The pH influences the strength of the effect: a lower pH causes greater action.¹²

Free Acids

The acid in alpha-hydroxy acid preparations may be free or it may be partially neutralized or buffered. In solution, alpha-hydroxy acids are present partly as free acid (neutral molecules that penetrate skin) and partly dissociated as the anion (charged molecules that do not penetrate skin).⁶

Types of Acid

The alpha-hydroxy acids include glycolic acid, lactic acid, mandelic acid, malic acid, citric acid, and tartaric acid, which occur naturally in sugarcane, sour milk, apples, grapes, and citrus fruit, respectively. They are more active in stimulating cell renewal, and others are more irritating.⁶ The activity depends on the length of the carbon chain, with longer chains showing diminished activity but greater moisturizing capacity.¹²

Vehicle

Because all commonly used alpha-hydroxy acids are water soluble, creams and lotions of oil-in-water emulsions are usually preferred. The most appropriate vehicle for a given product will depend on the purpose of the product and the patient's skin type.⁶ The vehicles may be: (a) hydro-alcohol-glycol solutions, indicated for oily and acneic skins because they have greater solvent capacity; (b) gels, also for oily and acneic skins, but also used for dry and mature skins; and (c) creams or creamy lotions, ideal for dry, dried and mature skins.⁴

Duration of Exposure

The penetration depth depends to a large extent on the length of time the acid is in contact with the skin.⁶

Patient Skin Type

Variables such as skin color, thickness, oiliness, laxity, fragility, and inflammation may also influence the effect of alpha-hydroxy acid products on the skin.⁶

Indications for Alpha-Glycolic Acid Peels

Hydroxy acid products include cleansers, moisturizers, toners, masks, age-spot removers, and other preparations.^{6,15} Initially, they were only used for the treatment of ichthyosis and other dry-skin conditions.⁶ These preparations moisturize dry skin on the face and body, decrease fine lines and wrinkles, improve skin tone and texture, and restore a radiant, youthful glow to the skin.^{6,17} The cosmetic products developed as astringents and exfoliates diminish skin scales and remove excess skin oil.¹⁷ There are many indications for a glycolic acid peel. Generally the most common is facial rejuvenation or an improvement in the appearance of the skin. Also, alpha-hydroxy acid products have been used successfully in combination with other therapeutic agents in treating hyperpigmentation, acne, actinic keratoses, ichthyosis, xerosis, psoriasis, seborrheic keratoses, pseudo-folliculitis barbae, chronic dermatitis, and erythema post-sunburn.⁶

Photoaging

Dramatic improvement of the fine lines and skin discolorations shown by the hard and thickened sun-exposed epidermis occurs with skin care that incorporates alpha-hydroxy acid products. With regular application, the outer signs of intrinsic and extrinsic aging decrease. Exfoliating dead cells makes wrinkles appear less deep.⁶ The long-term effects of alpha-hydroxy acids on the rate of exfoliation are not known, but research shows that the skin does become used to the stimulatory activity of alpha-hydroxy acids, with respect to measures of cell shedding.^{6,10}

Hyperpigmentation

Melasma is a genetic condition characterized by the appearance of brown patches, most commonly on the cheeks and/or forehead. Bleaching agents, such as hydroquinone (2%), are prescribed with good results for this type of hyperpigmentation, and combination therapy with glycolic acid (10%) has been found to be more effective than hydroquinone (2%) alone.⁶

Acne

Although acne results from multiple factors, an abnormal pattern of keratinization is believed to be one of the more important mechanisms. The ability of alpha-hydroxy acids to diminish corneocyte cohesion and keratinocyte plugging addresses this mode of acne pathogenesis. Lower concentrations reduce follicular corneocyte cohesion, thereby dislodging comedones and preventing their formation; higher concentrations cause unroofing of pustules and loosening of the keratinocytes that line the follicular epithelium.^{6,18} Acne responds quite well to short application of serial gly-

colic acid peels, which can be an important adjunct to therapy with topical and oral antibiotics.

Other Indications

Precancerous conditions, such as actinic keratoses, respond well to treatment with alpha-hydroxy acids, especially with glycolic acid peels. It can be applied in combination to 5-fluorouracil (5-FU).⁶ Flat warts, as well as mild acne scarring, may be treated with this peel. Superficial rhytides may also improve with the use of serial glycolic acid peel, depending on the skin type and individual patient response. Ichthyosis is a congenital disorder of keratinization characterized by dryness and fishlike scaling of the skin. It is effectively treated with formulations containing up to 12% glycolic acid, lactic acid, and their derivatives.⁶ Hyperkeratosis palmaris et plantaris can be successfully treated with short-term 70% glycolic acid application to the palms and soles.¹⁹ Xerosis is a common dermatologic condition in which the skin becomes rough and covered with fine, white scales. Studies have shown that alpha-hydroxy acid preparations at higher pHs (those that have been partially neutralized) reduce dry skin somewhat better and faster than lower pH preparations.⁶

Complications

There are many potential complications seen in any kind of chemical peel. These include, in order of severity: scarring, infection, post-inflammatory hyperpigmentation, post-inflammatory hypopigmentation, and persistent erythema.²⁰⁻²²

Retinoids

Retinoids include natural and synthetic compounds derived from retinol that show vitamin A activity.⁵ The importance of this vitamin became manifest many years ago, when xerophthalmia was widely observed in people with a diet poor in this vitamin. Some experiments on animals showed that dietary deficiency of vitamin A causes, among other things, an increase in epidermal keratinization and desquamating metaplasia of the mucous membranes.¹ The therapeutic action of vitamin A was tested on acne and psoriasis. In 1943, acne treatment was instituted with this substance. In 1952, Frey and Schoch²³ reported initial findings on the effects that this substance has in psoriasis because subtoxic doses of the vitamin induced peeling of the stratum corneum. In 1962, it was demonstrated that a physiologic acid derivative of vitamin A, all-trans-retinoic acid, can be used as therapeutic agent in dermatology. In 1955, isotretinoin, or 13-cis-retinoic acid, was synthesized but its therapeutic use only began in 1976. Etretinate was synthesized in 1972 and is used in the treatment of conditions associated with keratinization disorders.²⁴ Kligman and colleagues published the first study suggesting that topical

tretinoin was effective in the treatment of human photoaging.^{24,25} More recently, trials have been conducted with acitretin, the active metabolite of etretinate, a substance with fewer side effects because it does not accumulate in the deep compartments of the body and is therefore more rapidly eliminated.²⁴ Vitamin A is essential for normal skin-cell proliferation and regulation. The introduction of topical and then oral retinoids in the treatment of skin disorders two decades ago began a new era in dermatological therapy.¹⁷ Natural vitamin A is known as retinol, an alcohol that is converted to retinal, an aldehyde, which in turn is converted into retinoic acid. Retinal can be converted to retinol again, but retinoic acid is a dead-end metabolite and can not be recycled back up the chain. Retinal is an essential part of rhodopsin, the optic chromophore.¹⁸ Retinoids, such as isotretinoin (13-cis retinoic acid), etretinate, and acitretin, can be given orally for the treatment of skin diseases that cover large surfaces or areas not responsive to local treatment. Topical retinoids currently available include retinol, retinaldehyde, retinoic acid, isotretinoin, adapalene, and tazarotene.²⁶⁻²⁸

Pharmacology

Vitamin A is a 20-carbon molecule that consists of a cyclohexenyl ring, a side chain with four double bonds (all arranged in trans configuration), and an alcohol end group (all-trans retinol). The oxidation of the alcohol end group of all-trans retinol results in the formation of an aldehyde (all-trans retinaldehyde), which can be further oxidized to carboxylic acid (all-trans retinoic acid = tretinoin).²⁸ All-trans retinol cannot be synthesized in the body and is thus an essential nutrient. Retinyl esters and beta-carotene are the two major precursors of retinol in our diet. They are converted to all-trans retinol in the intestine and stored in the liver after reconversion to retinyl esters. Meals, particularly those with fat content, improve retinoid absorption. Because of its lipid solubility, etretinate has extensive and prolonged storage in fat resulting in a serum half-life of 80-160 days.²⁷ Upon discontinuing the drug, a low level may be detected in the blood for 2 years or more.²⁹ Retinol released from the liver is carried in the circulatory system by plasma retinol-binding proteins. It is removed apparently through passive diffusion.²⁸ Retinol is a hydrophobic molecule and it associates intracellularly with the cellular retinol-binding protein (CRBP). Thus, retinol can be metabolized to at least four important products: retinyl esters, all-trans retinoic acid, 14-hydroxy-4,14-retro retinol, and all-trans 3,4-didehydroretinol, and also its esters.²⁸

Mechanism of Action

The mechanism of action of retinoids has not been completely elucidated, but these substances have profound effects on the modulation of cellular proliferation

and differentiation.^{5,26,30,31} Retinoids have been demonstrated to exert anti-inflammatory effects in cutaneous diseases.²⁶ They are also considered as mediators of morphogenesis and development. These pleiotropic effects are known to be mediated by the interaction of retinoids with specific nuclear receptors that belong to the steroid/thyroid/vitamin D receptor superfamily.³⁰ There are specific retinol and retinoic acid receptors: the retinoic acid receptors (RAR α , RAR β , and RAR γ) are ligand inducible trans-acting factors that heterodimerize with the 9cisRA receptors (RXR α , RXR β , and RXR γ) and interact with specific DNA sequences or retinoic acid response elements contained in the promoter region of target genes.^{28,30-32}

Types of Retinoids

Oral Retinoids

Isotretinoin, etretinate and acitretin are used for skin diseases unresponsive to topical treatment or that affect large areas.^{26,27}

Topical Retinoids

Topical retinoids include retinol, retinaldehyde, retinoic acid, isotretinoin, adapalene, and tazarotene.^{26,27}

Isotretinoin

Isotretinoin acts in the normalization of the keratinization process of the follicular epithelium, reduces the number of sebocytes with decrease in sebum synthesis and reduction of the population of Propionibacterium, a microorganism that produces inflammation in acne.^{5,16}

Etretinate

Etretinate is used to treat psoriasis and is stored in adipose tissue. It probably promotes the terminal differentiation, normalizing the expression of keratin in epidermal cells; suppresses chemotaxis; decreases the cohesiveness of the stratum corneum; and may interfere with cytokine function.⁵

Acitretin

Acitretin has a plasmatic life of 50 hours. Similarly to etretinate, it does not accumulate in the adipose tissue or in the hepatic cells, where they show fat degeneration. It is better absorbed when ingested with a high fat.

Tretinoin

Tretinoin is a derivative of vitamin A called all-trans retinoic acid. Its primary effect is the reduction in hyperkeratinization that leads to the formation of microcomedones, the initial acne lesions. The bonds between the follicular corneocytes become looser as a result of the loss of desmosomes, decrease in tonofilaments, increase in keratinocyte autolysis, and intracellular gly-

cogen deposition.^{5,16} In the epidermis, they increase the thickness of the granular layer, decrease the strength of the tonofilaments and desmosomes, decrease melanocyte activity, and increase secretion of a substance similar to glycosaminoglycans in the intercellular space. In the dermis, blood vessel dilation was reported along with angiogenesis and increase in collagen synthesis in dermal papillae.^{25,26}

Retinol

Retinol is used for the treatment of skin aging in a concentration of 0.075%. There are no studies comparing its effectiveness with that of retinoic acid, although retinol does not appear to be as effective. There are indications that its beneficial effects would be greater at higher concentrations.

Retinoic Acid

Retinoic acid is used at 0.025%, 0.05%, and 0.1% concentrations for acne and photoaging treatment.

Retinaldehyde

Retinaldehyde is used at a 0.05% concentration for photoaging treatment. Its efficacy is similar to that of retinoic acid. It can be used for the treatment of acne, rosacea, seborrheic dermatitis, and also for the prevention of topical-steroid-induced atrophy.

Topical Isotretinoin

Topical isotretinoin is available in concentration of 0.05% for the treatment of acne. Its efficacy is similar to that of retinoic acid, producing less irritation.

Adapalene

Adapalene is a synthetic product analogue to retinoic acid. It belongs to the naphthoid acid derivatives family, which possesses high stability toward light and oxygen. Used in a concentration of 0.1%, its activity for moderate acne is similar but much less irritant than 0.025% retinoic acid.

Tazarotene

Tazarotene is a synthetic product that is also analogue to retinoic acid and belongs to the family of acetylenic retinoids. It has a specific binding profile to RAR-beta and gamma and is available at a concentration of 0.05% in a gel formulation for the treatment of mild psoriasis.

Retinoid Indications

Creams are more appropriate for sensitive skin and gels are appropriate for oily skin. The disadvantages of these products are that they may cause desquamation, burning and erythema, exacerbate preexisting lesions, and cause photoirritation with sunlight.^{14,16}

Complications

Some complications may be associated with retinoids, especially if used as oral an treatment.

Mucocutaneous

Generalized xerosis, scaling, retinoid-induced dermatitis, excessive growth of fine hair and kinking of the hair, nail changes, and others.^{26,33,34}

Ocular

Conjunctivitis, night blindness, myopia, and corneal opacities.³⁵

Serum Lipids

Increase in triglycerides and plasma cholesterol.^{26,35}

Hepatic

Elevation of transaminases, bilirubin and lactic dehydrogenase, decrease of albumin levels, toxic hepatitis.^{26,35}

Teratogenicity

This is the most important side effect of retinoids, and all physicians must be aware of it. Some authors have shown that pregnancies coinciding with retinoid treatment may result in normal births, spontaneous abortion, premature births, and congenital malformations. The site of action of the teratogenic effect may be the cells of the neural crest, indicating that the malformations are probably not related to the dose of the drug but to the gestation phase in which the embryo is exposed to the substance.³⁵ Maternal ingestion of retinoids early in pregnancy can lead to fetal abnormalities, and exposed infants seem to have a characteristic appearance. It is important that women are not pregnant before starting treatment³¹ and also that there is effective contraception during the therapy. The manufacturers recommend that conception should not occur for 1 month after isotretinoin therapy and 2 years after cessation of acitretin therapy,^{31,35} but there are recommendations for a total of 3 years after etretinate and acitretin.²⁹ There are no reports of impairment of spermatogenesis with isotretinoin or etretinate. They do not damage the human germinal epithelium when administered in therapeutic doses. Some males treated with etretinate have complained of impotence, but it is not clear whether the drug was responsible for this disturbance.³⁵ Man can safely father children when they are taking the drug.³¹

Conclusion

Glycolic acid and other members of the alpha-hydroxy acid family occur naturally in foods and have been used for centuries as cutaneous rejuvenation therapy. Recently, glycolic acid has proved to be a versatile peeling

agent and it is now widely used to treat many defects of the epidermis and papillary dermis in a variety of strengths, ranging from 20% to 70% depending on the condition being treated. The introduction of retinoids in the treatment of skin disorders two decades ago began a new era in dermatology therapy. Oral and topical tretinoin are widely used in the treatment of acne and photoaging. Research on acne pathogenesis has provided a rational basis for its use. Before instituting treatment with retinoids, the dermatologist must weigh the risks and benefits in each case. Though certain mild conditions may improve under retinoid therapy, the use of these drugs may not be advisable if the side effects are likely to outweigh the benefits. On the other hand, retinoids may have a more rapid effect on certain pathological processes than long-term treatment with other substances. Both drugs have multiple therapeutic indications when well prescribed. An excellent efficacy can be obtained in the treatment of many dermatoses using derived products that have been the subject of much research in recent decades.

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