ALPHA HYDROXY ACIDS
IN COSMETIC DERMATOLOGY

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_____ Synopsis

AHAs, the latest class of cosmetic active ingredients, are the focus of extensive research and many expectations. This paper deals with their chemistry, physiological activity and properties and possible therapeutic effectiveness in Cosmetic Dermatology.

_____ Riassunto

Ultima classe di principi attivi di uso cosmetico, gli alfaidrossiacidi sono al centro di molte ricerche e di molte attese. Ne viene descritta la composizione chimica, il probabile meccanismo d'azione e le varie possibilità di impiego nella Dermatologia Cosmetologica.

Much has been said about alpha hydroxy acids (AHAs). The latest class of active ingredients currently used in the cosmetic industry is the focus of many expectations and extensive research. That is the reason why they deserve to be dealt with in a detailed manner, so that dermatologists, plastic surgeries and beauticians can give their customers expert advice on this matter. AHAs are used both in dermatology and in cosmetic surgery as a supplement to standard medical therapy. In addition, their capacity to facilitate cell turnover is by now widely accepted. Let's see how they act in patients with xerosis, hyperkeratosis, acne and dehydrated skin. (1-10)

Keratinization consists in the malpighian epithelium undergoing changes. This results in the transformation of keratinocytes into corneocytes, external cells which are removed from the skin surface due to desquamation.

Before being removed, corneocytes carry out a protective and elastic action, which consists in making the epidermis compact, semi-permeable, flexible and soft. (11)

In patients with keratogenesis disorders, dermatologic events occur which lead to hyperkeratinization. Skin dryness, ichthyosis, keratosis and comedones are different disorders of similar nature: they are all associated with hyperkeratinization caused by increased corneocyte cohesion with a subsequent decrease in interstitial water. Increased corneocyte cohesion, which is linked also to the presence of intercellular lipids, leads to a greater number of more external cell layers. (12)

The resulting presence or lack of water, a main intercellular lubricant, as well as qualititative and quantitative lipid changes affect not only the physical properties, but also the scaling capacity of the stratum corneum. (13)

This pluricellular layer is generally characterized by a high capacity to absorb water, as in natural sponges. In addition, it can bind and retain water through NMFs and polar lipids, both of which are found in intercellular spaces.

Thus, corneocyte cohesion can be reduced by ensuring that both water in the stratum corneum and intercellular lamellar lipids, which control and regulate water diffusion, are constantly present. In order to treat hyperkeratinized skin, it is necessary to re-hydrate the stratum corneum using active ingredients which are able to bind water over long periods and subsequently reduce corneocyte cohesion. (14-19)

In fact, corneocyte cohesion depends on the moisture level, that is on water.

This decreased cohesion may also be due to a different arrangement of ionic bonds. The resulting biochemical process might be linked to the non-formation of the cross-linking extracellular matrix proteins, which usually trigger the events leading to keratinocyte and corneocyte cohesion. (1-2)

According to another hypothesis by Ziboh, it seems possible that an elevation of AHAs by dietary or topical means could suppress the cutaneous inflammatory reactions elicited by excessive generations of prostaglandins and leukotriens. (20)

In fact, the skin is characterized by an active metabolism of polyunsaturated fatty acids, the lack of which is known to cause dermatosis and skin barrier changes. Thus, a link is supposed to exist among AHAs, polyunsaturated fatty acids and skin cell metabolism. (20)

The concurrent therapeutic use of the gamma linolenic acid both topically and systemically is interesting also for the above reasons. (21)

AHAs:
CHEMISTRY AND ACTIVITY

Alpha hydroxy acids (AHAs), also known as alpha hydroxyenoic acids, are used in Cosmetic Dermatology. They are a peculiar group of biologically ubiquitary organic acids, since they play a specific role in the cycle of carbohydrates and other metabolic pathways (Table 1).

Among the many active ingredients currently known, alpha hydroxyenoic acids undoubtedly

have proved the most effective regulators of corneocyte cohesion. They facilitate water absorption among cells at the outer layers and reduce corneocyte cohesion at the lower layers of the stratum corneum, changing lipid typology and the enzymatic systems produced by Odland's lamellar bodies. As a result, a higher skin moisture level, improved cell turnover and normalization of keratoses and pigmentary abnormalities (Fig.1 a/b).
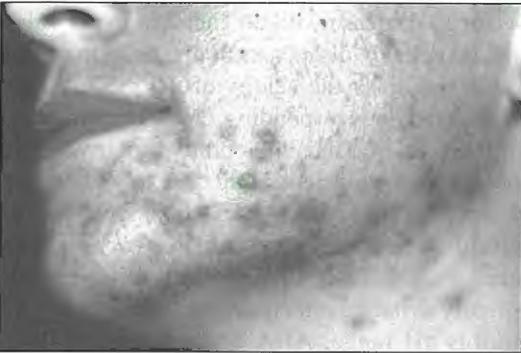

Fig. 1a - Before glycolic acid treatment

Fig. 1b - After one month treatment
(by courtesy of Dr A. Corbo - Rome)

The most biologically significant AHAs are usually found in nature and are regularly taken through food. Glycolic acid is contained in cane sugar, lactic acid in milk, malic acid in apples, citric acid in many citrus fruits, and tartaric acid in grape wine.

As can be noticed (Tab.1), AHAs belong to a family of chemical derivatives with different mo-

lecular weights, due to the varying length of their carbon chain.

Glycolic acid is made up of two carbons only, while, for example, citric acid contains six of them. We can easily understand why glycolic acid has a higher penetration degree than other alpha hydroxy acids with greater weight and size. However, we should not be misled by this. For example, the carbon lactic acid has also the biological capacity to convert into its ketonic form, namely piruvic acid, which is as much active in reducing corneocyte cohesion. (22)

There are added problems, such as the possible salification of these acids, which is often useful or even necessary to reduce their stinging or burning action on the skin and their reactivity to other molecules in cosmetics. As regards active ingredients, we should not forget that their skin penetration speed and ways depend not only on their molecular size, but also on their chemical and physical characteristics, on the formulation type, and thus on the vehicle which contains them and from which they should be released. It was shown why some AHAs mixtures act more rapidly than single compounds in both reducing corneocyte cohesion and improving the skin hydration state. The optimum pH value, at which they appear extremely active, was shown to range from 4 to 5.5. (23-26)

In addition, standard moisturizers, such as collagen, appeared to be active over some hours only, while AHAs administered topically and gelatin-glycine administered both topically and

Tab 1

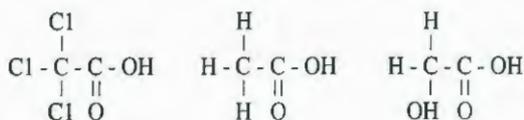| Glycolic acid	OH $CH_2\text{-}COOH$	mw 76,05
Lactic acid	$CH_2\text{-}CH\text{-}COOH$ OH	mw 90,08
Malic acid	$HOOC\text{-}CH\text{-}CH_2\text{-}COOH$ OH	mw 134,09
Tartaric acid	$HOOC\text{-}CH\text{-}CH\text{-}COOH$ $OH\ OH$	mw 150,09
Mandelic acid	$CH\text{-}COOH$ OH	mw 152,14
Citric acid	$COOH$ $HOOC\text{-}CH_2\text{-}C\text{-}CH_2\text{-}COOH$ OH	mw 192,12

systemically, act over long periods (days), even when they are temporarily discontinued. Finally, the action of AHAs was shown to be directly proportional to their concentration, which depends on the vehicles used. (27-28)

Although its mean of action is still unknown, current data seem to indicate that AHAs activity consists in decreasing corneocyte cohesion through a modification of ionic bonds.

When applied locally at low concentrations (10-12%) using suitable vehicles, AHAs gradually make hyperkeratinized stratum corneum less tough by reducing corneocyte cohesion at the lower level of stratum corneum without affecting the upper cells level, directly in contact with the outside.

When applied at high concentrations as, for example, in peeling treatments (70% glycolic acid), they cause no disaggregation of corneocytes in the outer layers of the stratum corneum, as happens when using other chemical agents such as strong acids and alkali, including trichloroacetic acid, thiols or other denaturants (urea and lithium salts at high concentrations).

Unlike what happens with the above actual keratolitics, AHAs affect the cohesion of newly-formed corneocytes in the lower layers. In fact, glycolic acid is structurally similar to both trichloroacetic acid and acetic acid:

$$Cl-\overset{\overset{\displaystyle Cl}{|}}{\underset{\underset{\displaystyle Cl}{|}}{C}}-\overset{\overset{}{}}{\underset{\underset{\displaystyle O}{||}}{C}}-OH \qquad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}-\overset{}{\underset{\underset{\displaystyle O}{||}}{C}}-OH \qquad H-\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}}-\overset{}{\underset{\underset{\displaystyle O}{||}}{C}}-OH$$

Trichloroacetic acid   Acetic acid   Glycolic acid

Glycolic acid shows an intermediate acidity with respect to the other two acids, due to the presence of the -OH hydroxyl group in its molecule. Thanks to its small molecular size, it penetrates the epidermis and probably also the dermis. Due to its acidity, it brings about an intraepithelial chemical peeling, reducing the cohesion power

that bind corneocyte together. (29) This peculiar way of acting suggests that their dynamic pharmacological action is carried out only at a specific stage of the keratinogenic process.

pH VALUE AND CELL TURNOVER

When being in their acid form and at suitable concentrations (5% to 10% approx.), AHAs increase cell turnover: their stimulating capacity seems to decrease with the increase in pH value and completely disappears at pH 7. On the other hand, the lower the acidity of the medium, the stronger the corresponding erythemic property of these acids. Thus, the optimum pH value for AHA-based emulsions is thought to be between 4 and 5.5. In fact, at pH 4.5 the amount of free glycolic acid is still great and, in any case, sufficient to effectively stimulate cell turnover with slightly irritating effects on the skin.

In this pH range, AHA erythemic property is thought to be reduced to its minimum, without affecting the action AHAs seem to carry out on the proteic bonds that desmosomes establish with epithelial cells. The dissolution of these bonds due to a low pH value seems to underlie the increase in DNA synthesis and in the metabolism of the skin cells subject to AHA action. (29)

SYNERGIC SUBSTANCES

According to recent studies, gelatin-glycine and gelatin-arginine seem to be able to synergize the re-moisturizing activity of AHAs. Concurrently using gelatin-glycine both topically and systemically allowed to reduce AHA dosage and to improve AHA re-moisturizing activity, positively effecting "wrinkle lines" due to photo-ageing. Concurrently using these two active ingredients reduces AHA risk-benefit ratio and prevents the so-called *status cosmeticus* sometimes caused by the low pH value of these acids.(30)

AHA CONTROLLING SKIN HYPERKERATOSIS

Much clinical importance is attached to the laboratory finding that, repeatedly applying AHAs at low concentrations, prevents a thick stratum corneum from re-forming, after this has been eliminated by previous intensive treatment (such as peeling). This is a way to treat skin disorders in a relatively short time. (31)

This enables to effectively use AHAs with periodical follow-up of treatment for xerosis, ichthyosis, acne and ageing-related actinic keratosis (the so-called *age spots*), also in order to keep wrinkle-prone skin smoother and firmer. (26-28, 32-34)

If applied in consulting rooms at high concentrations, AHAs penetrate deeper in the skin with a probably less specific effect. They cause reduced keratinocyte cohesion, complete epidermolysis, epidermis separation and heavy stimulation of the dermis, both papillar and reticular, with resulting deep injuries. Thus, the ideal conditions occur that seem to underlie the synthesis of new collagen. (35-37)

This activity naturally and directly depend on the skin area and type, on the pH and AHA concentrations, on the type of vehicle, the exposure time and the cleansing methodology. The clinical relevance of the changes resulting from the use of AHAs at high concentrations indicates that they should be administered exclusively by dermatologists.

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