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Current Review of the Alpha-hydroxy Acids

Alpha-hydroxy acids (AHAs) are naturally occurring organic carboxylic acids such as glycolic acid, a natural constituent of sugar cane juice *and lactic acid, found in* sour milk *and* tomato juice. *Topical formulations incorporating these acids are now frequently used or prescribed by dermatologists and they are also present in a wide range of heavily promoted cosmetic products. The growth in sales of these products has been phenomenal. Back in 1994, sales of two products totalled $300 million dollars,[1] and by 1996 more than 45 companies were manufacturing over 200 different AHA-containing products.[2]*

Few could have forecast the impact that the research on these compounds, initiated by Van Scott and Yu twenty years ago[3], would have on the practice of dermatology and the product range promoted by the cosmetic industry. Since then, Van Scott and Yu, together with other investigators have :

- Determined that AHAs are useful for dry skin and photodamaged skin.
- Found that AHAs can be used by dermatologists in office procedures (e.g. chemical peels).
- Contributed to development of a gluconolactone formulation. This polyhydroxy AHA appears to be better tolerated by sensitive skin.
- Played a watchdog role by commenting on unfounded performance claims made for a number of cosmetic products containing AHAs, and attempting to correct what they believe to be erroneous information and incorrect statements made in articles about AHAs.

Dr. Stuart Maddin, Editor

Mechanism of action

AHAs exfoliate dead skin cells and moisturize the skin.[4] Their main action is to facilitate desmosomal degradation leading to an increase in corneocyte desquamation, an increase in cytokines and increased epidermal proliferation.[5] There is also as an increase in hyaluronic acid (which holds 1000x times its weight in water)[5,6] and this might be one of the causes of increased skin 'plumpness'.[6] By normalizing corneocyte cohesion, the stratum corneum is thinned and smoother and more flexible (even at low relative humidity[7]), and the formation of dry flaky scales is reduced .[8] The overall result is skin which looks and feels better.[8]

Claims that AHAs reverse photodamage and reduce wrinkles, brown spots and roughness are somewhat controversial and are currently being reviewed by the Cosmetic, Toiletry and Fragrance Association (CTFA), the FDA and the Federal Trade Comission (FTC).[4] Several aspects concerning the mechanism of action of AHAs are still unknown. In particular, little is known about the correlation between the histopathological and functional changes in the stratum corneum induced by AHA treatment.[8] Studies have suggested that treatment with AHAs produce significant reversal of epidermal and dermal markers of photoaging.[9]

Therapeutic use

The end use is critical – is it to be used as a cosmeceutical, a dermatologic application or as a chemical peel?[10]

Formulation is more important than concentration alone.[5] Bioavailability of the AHA is a major determinant; for example a high concentration of AHA near neutral pH is ineffective because the bioavailability

is miniscule. At the other extreme, at low pH even small concentrations can be effective because a major amount of the AHA is available.[6] The more free acid, the more biologic activity.[5]

An Expert panel of the US Cosmetic Ingredient Review (CIR) concluded in 1996:

- AHAs are safe in cosmetic products at concentrations of 10% or less, at a pH of 3.5 or greater, and formulated to avoid increasing the skin's sensitivity to the sun or accompanied by directions to use sun protection daily.
- Stronger formulations of AHAs (concentrations up to 30% and a pH as low as 3.0) are safe if applied by trained professionals. Such use should be brief, discontinuous, and followed by thorough rinsing and accompanied by directions to use sun protection daily.[11] Stronger concentrations are sometimes needed for the thickened stratum corneum seen in some dermatologic diseases.[12]

When formulations of AHAs are to be applied daily, chemical buffering or partial neutralization are important to ensure skin tolerance,[6,12,13] but to maintain the AHAs activity, buffering agents should not bring the pH above four.[5] Formulations used for peeling purposes perform best when the AHA is completely bioavailable at its native low pH.[6]

Adverse effects

AHAs are acids and can cause mild to moderate irritation unless they are neutralized in the final product. Low concentrations of AHAs appear to be less irritating than tretinoin, and no other adverse effects have been reported, but long-term studies have not been done.[14] As is the case with tretinoin[3], AHAs can sometimes cause stinging/burning in nasolabial and sub-orbital areas and local contact irritation.[5] If an acid peel has been accomplished using glycolic acid, then photosensitivity is a concern for about two weeks after the peel.[12] In any case, sunscreen and sunblock agents should always be used to protect against solar damage.[6]

Future developments

Although glycolic and lactic acids are the two AHAs that we have had the most clinical experience with, other AHAs have properties which might make them suitable for specific uses.[6]

AHAs place in therapy

AHAs are the introduction of science to the cosmetic field, and for the first time in the cosmetic industry an ingredient is active and has profound beneficial physiologic effects.[13] Previously, many claims made for cosmetics were based more on marketing than on science.[12]

	AHAs	Tretinoin
Category	Cosmetics (non-drug category) Non-prescription	Prescription drug approved by regulatory agencies in the US & Canada for the topical treatment of acne and photoaging
Action	Modulate stratum corneum formation through diminished cellular cohesion between corneocytes.	Affects keratinocytes, melanocytes and collagen formation.
NOT useful	The usefulness of AHAs for *acne* is awaiting further confirmation.	For *dry skin, rosacea* or *some disorders of keratinization*.
USEFUL	For ***dry skin, ichthyoses***. *Photoaging* benefits are awaiting confirmation.	For ***acne vulgaris***, ***photoaging*** and ***hyperpigmentation***.
Choice	*Depends upon therapeutic objectives, combination use of both is often the most rational approach.*[5,6]	

With the AHAs, in deciding whether regulatory intervention or monitoring is necessary, the FDA and other agencies will examine the overall balance reached between use for scientifically justifiable indications, and misuse based on unproven, over-promoted claims.[6]

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FDA Warning about Isotretinoin
(Accutane®, Roaccutane®)

On the 26th of February 1998, Hoffmann-LaRoche, on the instructions of the FDA, sent out more than 210,000 Dear Dr. *warning letters to health care providers communicating new safety information about the prescribing of isotretinoin for acne, and citing isolated reports of drug-induced depression, psychosis and rarely, suicidal thoughts and action.*

Isotretinoin has been available since 1982 and prescribed to more than eight million patients in eighty countries.[1] The possibility of depression associated with the use of isotretinoin has long been recognized and has been mentioned in company provided information since 1986, but Hoffmann-LaRoche have agreed to a more prominent warning.

- *The WARNINGS section will now begin with the following paragraph in bold type:*

"Psychiatric disorders: isotretinoin may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of isotretinoin therapy may be insufficient; further evaluation may be necessary. No mechanism of action has been established for these events."

- *The paragraph on depression in the ADVERSE REACTIONS section will become paragraph five of that section and will be revised as follows:*

"In the post-marketing period, a number of patients treated with isotretinoin have reported depression, psychosis and, rarely, suicide ideation, suicide attempts and suicide. Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy." It is important to note that reports of these Adverse Experiences are uncommon but, because of their potential consequences, clinicians should be attentive to any new behavioral signs and symptoms.

- The FDA has also told Roche to change its medical journal advertisements for isotretinoin, saying they make false and misleading claims that it has a positive impact on psychosocial effects, such as depression, in patients with severe recalcitrant nodular acne. This material had previously been reviewed by the FDA and had been in use for more than one year.[2]

The FDA action was triggered by 20 Spontaneous Adverse Event Reports (SAER) submitted worldwide, of depression linked to the use of isotretinoin in which patients became better after being taken off the drug and then felt worse on rechallenge. Twenty reports since 1982, and yet over this period isotretinoin has been *prescribed to more than eight million patients in eighty countries*.[1] SAER reports are received by Regulatory Agencies worldwide (for example MedWatch in the US, CIOMS in other countries). They can be submitted by anyone and are not corroborated or validated. However, *"that pattern is enough for us to say that there is an association"* said Dr. Jonathan Wilkin, director of the FDA's Division for Dermatologic and Dental Drug Products. *"Even without causality, even without a mechanism, we think it is prudent to let physicians know about this. Further research should show whether the warning should eventually be strengthened or dropped,"* Wilkin said. This action of the FDA is consistent with regulations that read:

"*Warnings* Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved."

World experts polled for their opinions

I am very grateful to members of the Editorial Advisory Board to *Skin Therapy Letter*, and other world recognized authorities on acne vulgaris, for providing answers to the following questions.

Stuart Maddin, Editor.

Will the labeling changes reported in the recent Dear Doctor letter influence you in your future use of isotretinoin?

Yes 2 No 24

In the absence of more convincing evidence, almost all polled felt that the warnings included in the Dear Doctor letter will not alter their prescribing habits.[3]

Does your experience with isotretinoin support the new warnings that are to appear on the label etc. ?

Yes 2 No 24

The answer is a resounding NO! A number of the experts polled state that severe, cystic acne itself can often cause patients to be very disturbed, and in some instances actually depressed, but in these patients when treatment is completed, their mood has returned to normal.[3]

One dermatologist polled had two private practice patients who became depressed but not suicidal when taking isotretinoin, whose depression cleared when treatment ceased,[4] a second had seen two patients with mild to moderate depression in approximately 18 years,[5] another had not seen marked mood swing, but about 6 out of some 5-600 patients treated with isotretinoin had depression.[6] *Discuss this side effect at length with patients, watch patients with a history of depression carefully, and consider alternative treatments when warranted.*[7]

The risk of depression or suicide due to the disease that is being treated with isotretinoin is more important than the risk due to isotretinoin itself.[8]

Can you recall any of your patients whose mood improved or who were less depressed following treatment with isotretinoin?

Yes 18 No 5

The majority of replies reflect the mood improvement associated with effective treatment of acne with isotretinoin.[3]

Many patients with acne are depressed, but their mood usually improves significantly after isotretinoin treatment[5,9,10] simply because treatment has been successful.[8,9] Seeing early improvement in their acne cheers patients up enormously [6,11,12] and improves their self image.[7]

Experts polled:

Arndt Dr. KA	Harvard Medical School, Boston, US
Bergfeld Dr. WF	Cleveland Clinic, Cleveland, US
Berson Dr. DS	NYU, New York, US
Bos Prof. J	University of Amsterdam, Netherlands
Caputo Dr. J	University of Milan, Italy
Cunliffe Prof. WJ	The General Infirmary, Leeds, UK
Degreef Prof. H	Catholic University, Leuven, Belgium
Dobson Dr. RL	Medical University of South Carolina, US
Faegermann Dr. JN	University of Gothenburg, Sweden
Gilchrest Dr. BA	Boston University School of Medicine, US
Goh Dr. Chee Leok	National Skin Centre, Singapore
Gollnick Prof. HPM	Otto von Guericke University, Germany
Griffiths Dr. WAD	St. Johns Institute of Dermatology, London, UK
Ho Dr. VCY	University of British Columbia, Vancouver, Canada
Katsambas Prof. AD	University of Athens, Greece
Kligman Dr. A	University of Pennsylvania, US
Leyden Dr. JJ	University of Pennsylvania , US
Mascaro Prof. JM Clinico,	Department of Dermatology, Hospital Barcelona, Spain
Orfanos Prof. CE, Zouboulis Prof. Dr. CC	Freie Universitäts, Berlin, Germany
Plewig Prof. G	University of Munich, Germany
Saurat Prof. Jean-Hilaire	Cantonal Universitaire, Geneva, Switzerland
Shalita Dr. AR	SUNY Health Sciences Center, Brooklyn, US
Strauss Dr. J	University of Iowa, US
Thestrup-Pedersen Prof.K	University of Aarhus, Denmark
Thiboutot Dr. DM	Pennsylvania State University, US
Wolff Prof. K	University of Vienna, Austria

Relevant Worldwide Spontaneous Adverse Event Reporting (SAER) of Isotretinoin

Suicide attempt reports received by SAER: 47
(until March 15, 1998)

Since about 80% of cases of attempted suicide received in association with isotretinoin had known risk factors or an unlikely temporal relationship reported, a causal relationship to isotretinoin treatment cannot be established.[13]

Suicide reports received by SAER : 38
(until March 15, 1998)

Approximately 80% of patients who committed suicide in association with isotretinoin therapy had a relevant medical history known to be associated with depression and an increased risk for suicide and/or had an unlikely temporal relationship documented, and a causal relationship between isotretinoin to suicide cannot be established. Cases may well reflect the background incidence of this frequent disorder.[14]

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Rates of depression, suicide attempts, and suicide are much lower in patients taking isotretinoin than in the general population. The expected rate of depression in the general population is 5-14% compared to 0.018% in patients taking isotretinoin. Even if 0.018% were a gross underestimate, it is still much lower than would be expected. The magnitude of discrepancy is similar between expected rates of suicide attempts and suicide in the general population, and actual rates in patients taking isotretinoin.[15]

Psychosis reports received by SAER:
150 cases, 178 events *(until November 30, 1997)*

Approximately two thirds of patients who experienced psychotic events in association with isotretinoin had either a relevant psychiatric or personal history, a relevant co-medication or another relevant condition, family history or unlikely temporal relationship. In the remaining cases, there was often insufficient information to make a proper assessment.[16]

Depression reports received by SAER:
586 cases, 615 events *(until November 30, 1997)*

Analysis of cases of depression in association with isotretinoin treatment is not indicative of a causal relationship. The strongest confounder is the uncertainty about the prevalence of depression in acne patients. In addition, records noting onset of depression and timing of dechallenge are not reliable, half of the patients cited had other confounders reported and reaction after rechallenge was equally positive and negative.[17]

> We have known for a long time that isotretinoin can influence mood and that a high percentage of acne patients are depressed – some of them severely and that detection is difficult. *This recent FDA action makes it seem like something newly recognized, but this is not so.*[18]

Although a few patients may have reported some depression with isotretinoin, it is *infrequent*.[DB] Some of the experts polled remain unconvinced about the validity of the data[19] and feel the link to isotretinoin is unproven[20], some have never seen a patient developing a psychiatric disorder under isotretinoin therapy,[11] and others after ten years experience and taking into consideration the published literature will not be influenced by the FDA.[8] The possibility of treatment induced depression has been recognized for a long time and included in company provide information since 1986, and as long as this is kept in mind, isotretinoin remains an excellent drug.[19] Many patients who are extremely depressed about their acne and quite withdrawn have their whole outlook changed positively **after** isotretinoin treatment.[9]

When prescribing isotretinoin, as well as being concerned about the risk of teratogenicity, we now have to be alert to the possibility of drug-induced depression, psychosis and suicide. The risk seems small, but these decisions by the FDA and the resultant publicity have increased our management responsibility. Warning flags that should alert the physician include a previous history of altered mood (i.e. depression) or a history of taking mood altering or psychotropic drugs, or any suggestion of depression or psychotic behavior developing during treatment. If any of these warning signs are detected in the patient, consider the possibility of an isotretinoin induced effect and the need for increased monitoring or a change in the treatment plan.

Stuart Maddin, Editor

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
Actinic keratoses	**Diclofenac sodium** Solarase® Gel 3% *Hyal Pharmaceutical*	Approved in Canada, May 1998 for the topical treatment of actinic keratoses.
Antibiotic	**Trovafloxacin** (oral) **Alatrovafloxacin** (IV) Trovan® *Pfizer*	Recently approved by the FDA for 14 indications including skin and skin structure infections. This "fourth generation" quinolone is given once daily, orally or IV, and is active against penicillin-resistant pneumococci, gram-negative bacteria, atypical organisms and anaerobic bacteria.
Anti-HIV	**Zidovudine** 300 mg/ **lamivudine** 150 mg Combivir® *Glaxo Wellcome*	Approved by the EC Commision. Combivir aims to improve compliance by reducing the pill burden for HIV patients on combination antiretroviral therapy.
UV-induced skin discolorations	**Hydroquinone** 4%, **glycolic acid** & an **antioxidant complex.** Lustra® *Medicis Pharmaceutical*	Recently approved by the FDA for the treatment of photo-induced skin discolorations as well as hyperpigmentation associated with pregnancy, superficial trauma and the use of oral contraceptives and hormone replacement therapy.
New Developments		
Leprosy	**Leprosy vaccine**	Approved in India, this vaccine is said to be the first to stimulate the immune system to kill *Mycobacterium leprae*. It is administered intradermally, and given as an adjunct with standard multidrug therapy is expected to accelerate healing and reduce the duration and cost of therapy.
Scleroderma	**Minocycline** Minocin® *Lederle*	A preliminary report from workers in Boston suggests that minocycline may be of benefit in the management of scleroderma.
	New Side Effect	
Protease inhibitors	Lumps, humps and bumps of mature pockets of adipose tissue have been described in patients taking anti-HIV protease inhibitors, as soon as two months after starting therapy. These buildups of fatty tissue, which have been termed *protease paunches, buffalo humps, horsecollar buildups and Crix belly*, have been seen in patients taking all types of protease inhibitors.	

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