Mechanisms of Action of Azelaic Acid 15% Gel: Assessing Its Broad Antioxidant and Comedolytic Effects

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Two small studies were undertaken to investigate the ability of azelaic acid (AzA) 15% gel to function as a comedolytic and as a topical antioxidant. The first study compared AzA 15% gel with benzoyl peroxide (BPO) 5% gel as a comedolytic. Ten participants were randomized to apply AzA 15% gel on one shoulder and BPO 5% gel on the other shoulder twice daily for 4 weeks, with a nontreated site on the central back serving as the control in all participants. Comedone counts were obtained at baseline and week 4 by examination of cyanoacrylate biopsies taken from each site. The AzA 15% gel and BPO 5% gel produced substantial decreases in mean comedones (12 to 0.9 and 14.9 to 1.6, respectively) from baseline to week 4 as compared with controls (14.6 to 10.9).

The second study compared sunburn cell counts in AzA-treated skin versus untreated skin exposed to simulated solar radiation. Participants were randomized and applied AzA 15% gel to one buttock and nothing to the other buttock twice daily for 8 weeks. Both buttocks were then irradiated, and after 24 hours, punch biopsies were taken from each buttock. Sunburn cell counts were lower on the AzA-treated side in 7 of the 10 participants. Because AzA does not function as a sunscreen, this photoprotectant effect is probably due to antioxidant action.

If dermatologists were asked what single medication they would like to have if marooned on a desert island, many would say aspirin. Aspirin is a perfect example of a multiaction medication. It reduces inflammation, alleviates pain, and can prevent cardiovascular disease. Dermatologic medications can have a similar versatility of action. For example, tetracyclines are used for their antibacterial and anti-inflammatory qualities to treat acne. Sodium sulfacetamide and sulfur combinations are used for antibacterial, antifungal, and anti-inflammatory purposes for acne, seborrheic dermatitis, and rosacea. One could argue that versatile ingredients can often be more valuable than those that deliver a single, albeit powerful, effect.

An alternate dermatologic prescription that has multiple mechanisms of action is AzA 15% gel. Also known as nonanedioic acid, AzA is a saturated dicarboxylic acid found naturally in wheat, rye, and barley. It is also produced by the yeast *Pityrosporum ovale*, a natural component of the skin biofilm.

Exhibiting a broad spectrum of antimicrobial activity, AzA shows bacteriostatic and antibacterial action against *Propionibacterium acnes*, *Staphylococcus epidermidis*, and other aerobic microorganisms without inducing antibiotic resistance[1-4]; it normalizes keratin production[5]; and it decreases neutrophil generation of reactive oxygen species and inhibits lipoxygenase, which is involved in the formation of leukotrienes and eicosanoids, which are important inflammatory mediators.[6,7] These antibacterial, antikeratinizing, and anti-inflammatory properties of AzA 15% gel make it useful in the treatment of multifactoral disorders such as acne, rosacea, and seborrheic dermatitis. In addition, AzA acts on melanocytes to lighten skin dyspigmentation in disorders such as melasma and postinflammatory hyperpigmentation.[8-10] For patients experiencing more than one skin disorder, the ability to treat concomitant conditions with a single agent can also be a great advantage.

The current research was undertaken to better understand the specific functionality of AzA 15% gel as a comedolytic and as an antioxidant. Two study methodologies were designed and executed to clarify the extent to which AzA 15% gel possessed these qualities.

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TABLE 1

Comedone Counts for Sites Treated With AzA, BPO, and Untreated Site

Participant	Baseline AzA	Week 4 AzA	Baseline BPO	Week 4 BPO	Baseline Control	Week 4 Control
1	15	2	25	1	20	12
2	11	3	17	1	17	18
3	13	0	14	1	11	19
4	12	0	11	1	16	12
5	14	3	22	1	16	10
6	11	1	15	7	17	8
7	12	0	11	2	16	14
8	12	0	12	1	10	9
9	10	0	11	1	13	3
10	10	0	11	0	10	4
Mean Count	12	0.9	14.9	1.6	14.6	10.9

Abbreviations: AzA, azelaic acid; BPO, benzoyl peroxide.

Comedolytic Action of AzA 15% Gel

Acne is characterized by the presence of open and closed comedones, with BPO used as a standard medication to induce the elimination of comedonal plugs. Previous studies have shown that AzA 15% gel can reduce both inflammatory and noninflammatory lesions in acne,[11] and it has been approved since 2002 as an acne treatment in Europe. This study investigated the comedolytic effect of AzA 15% gel as compared with BPO 5% gel. Its aim was to histologically document the comedolytic action of AzA 15% gel and provide a quantitative measure of comedone reduction.

Method

This was a single-center, investigator-blinded, placebo-controlled study. Ten participants, aged 18 years and older, with a minimum of 10 prominent comedonal plugs on the upper right, middle, and left back, were enrolled following completion of an institutional review board–approved informed consent. Participants were prohibited from using any prescription or nonprescription acne treatments on the back for 4 weeks prior to study entry. The minimum comedone count was confirmed by performing cyanoacrylate biopsies at baseline of the right posterior shoulder, left posterior shoulder, and central back. The biopsies were obtained by placing one 6-mm drop of cyanoacrylate glue on a glass microscope slide and immediately positioning the slide on the back. The glue was allowed to dry for 20 minutes and gently lifted from the back. The comedonal plugs, which appeared as yellow, waxy inverted cones, were counted under a 1× dissecting microscope in a 1-cm^2 area. If 10 comedonal plugs were observed on each slide, the participant was entered in the study.

Participants were randomized to apply AzA 15% gel on one shoulder and BPO 5% gel on the other shoulder. The nontreated site on the central back served as the control in all subjects. Applications continued twice daily for 4 weeks, with compliance documented in a diary. Participants were only allowed to use bar soap on the back for cleansing, and no moisturizers or other skin care products of any type were allowed. Participants returned to the research center for repeat cyanoacrylate biopsies of the right, left, and central upper back in the area of product application. The same biopsy technique as employed at baseline was followed.

Results

All 10 participants completed the 4-week research study. No adverse events occurred during the administration of the study. The results are summarized in Table 1.

Discussion

At entry, the number of comedones in each of the study areas was similar, with an average of 12 in the AzA 15% gel areas, 14.9 in the BPO 5% gel areas, and 14.6 in the control areas. During the study period, the number of comedones in the control site did not change dramatically. It went from a mean count of 14.6 at baseline to a count of 10.9 at week 4. Both AzA 15% gel and BPO 5% gel produced substantial decreases in mean comedones (12 to 0.9 and 14.9 to 1.6, respectively), indicating that both substances are capable of inducing a comedolytic effect after 4 weeks of use on the upper back.

Antioxidant Action of AzA 15% Gel

The second study examined the ability of AzA 15% gel to function as a topical antioxidant. The antioxidant value of AzA 15% gel was assessed by using a standardized sunburn cell protocol. The sunburn cell assay measures the ability of a topical or oral substance to prevent cell death induced by UV radiation. Sunscreens with a high sun protection factor achieve this by blocking UV radiation, but sunburn cell formation can also be reduced by antioxidant action.[12] Even though AzA 15% gel has been shown in vitro to possess antioxidant action, it does not contain any sunscreen-type photoprotectants in its formulation.[6,7]

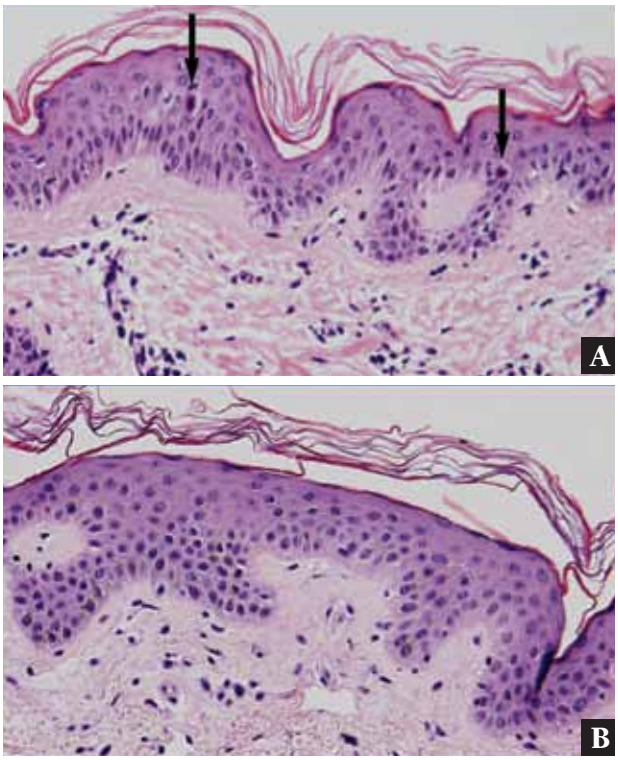
Method

Participants applied AzA 15% gel to a randomized right or left upper outer buttock and nothing to the same site on the opposite buttock twice daily for 8 weeks. Cleansing with bar soap and water was allowed, but other skin care products were not to be applied to the study sites. Only subjects with virgin, sun-protected skin on both buttocks were enrolled. Participants with a suntan from natural or artificial sources were not eligible for enrollment. All participants avoided sun exposure to the buttocks for the duration of the study. A compliance check occurred at 4 weeks.

Participants returned to the research center at 8 weeks for irradiation of both upper outer buttocks with a minimal erythema dose of 2 from a solar simulator, a 150 W xenon arc bulb. A partial-thickness, 3-mm punch biopsy was obtained from the treated and untreated sites 24 hours after irradiation. Specimens were formalin fixed and sent to a dermatopathology lab for hematoxylin and eosin staining and sunburn cell counts.

Results

Ten of 10 participants completed the study, and no compliance issues were noted from the study diary analysis.



Biopsy specimens from untreated skin, with dark pink sunburn cells in epidermis (A) and AzA-treated skin (B) of the same participant.

No adverse events occurred during the administration of the study. Sunburn cell counts were obtained by counting the apoptotic cells in three 3-mm sections taken from the center of the biopsy specimen for a total analysis of 9-mm linear tissue (Figure and Table 2).

Discussion

Seven of 10 participants produced fewer sunburn cells at the site treated with AzA 15% gel. Since AzA does not function as a sunscreen, and the sunburn cell study was conducted with clean skin, the mild photoprotective effect shown by AzA is probably due to antioxidant action. Specific antioxidant mechanisms of AzA, such as inhibition of reactive oxygen species generation by neutrophils and inhibition of the oxidation catalyst lipoxygenase, have been demonstrated in vitro and may at least partially account for the anti-inflammatory activity of AzA in treating rosacea, acne, and other skin conditions.[6,7]

The results of the research also confirmed that AzA 15% gel is not a phototoxic agent or a photosensitizer. These are important findings for a topical medication.

Summary

Multiplicity of action is a well-known concept in dermatologic medications adding to the versatility for usage. This

TABLE 2

Sunburn Cell Counts for AzA-Treated Site and Untreated Site

Subject	AzA-Treated Site	Untreated Site	Count Reduction With AzA
1	4	22	18
2	20	18	−2
3	5	23	18
4	51	74	23
5	13	18	5
6	87	55	−32
7	20	24	4
8	12	15	3
9	54	52	−2
10	20	31	11

Abbreviation: AzA, azelaic acid.

research has demonstrated in 2 small, controlled studies that AzA 15% gel can function as both a comedolytic and an antioxidant. As a comedolytic, it compares favorably with BPO, a standard acne treatment, and achieves comparable reductions in comedone counts. For those with concomitant conditions that AzA can also address, it might be preferred. As a topical antioxidant, AzA 15% gel shows some ability to mitigate photodamage in sun exposed skin. Antioxidant properties have previously been hypothesized to account for its anti-inflammatory action in rosacea, acne, and other skin disorders.

Dermatologists need to be aware of the possible multiple effects of the medications they prescribe, and they need to make their patients aware of them as well. In disorders of complicated etiology, such as rosacea, as well as in patients with multiple skin conditions, awareness of a drug's versatility of action may help increase confidence and compliance in its use. This work adds to our understanding of the utility of AzA 15% gel in the dermatologic armamentarium.

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