An Aluminum Magnesium Hydroxide Stearate-based Skin Barrier Protection Cream Used for the Management of Eczematous Dermatitis

A Summary of Completed Studies

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ABSTRACT

Eczematous dermatoses can often be very difficult to treat. An aluminum magnesium hydroxide stearate-based cream has recently become available for clinical use. Aluminum magnesium hydroxide stearate-based cream provides an alternative option in treating these dermatoses while providing barrier protection against external allergens and irritants. This article reviews various studies evaluating aluminum magnesium hydroxide stearate-based cream.
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Nonsteroidal therapeutic options are limited for the treatment of eczematous dermatitis involving the hands, including irritant contact dermatitis, allergic contact dermatitis, and atopic dermatitis. The availability of a nonsteroidal topical preparation capable of relieving symptoms of eczematous hand dermatitis, such as pruritus and burning, that may also provide protectant activity, would be a welcome addition to the therapeutic armamentarium. Such an agent could be used as a component of initial treatment, and, when more prolonged therapy is needed, in cases of greater chronicity.

Recently, a water-impermeable prescription cream (Tetrix®, Coria Laboratories, Ltd., Fort Worth, Texas) containing aluminum magnesium hydroxide stearate (AMHS) and several silicate derivatives (dimethicone, cetyl dimethicone, cyclomethicone), formulated as an aqueous emulsion, has been cleared by the Food and Drug Administration (FDA) and is available for clinical use. For the purpose of this discussion, this formulation will be referred to as AMHS-based cream. The AMHS-based cream is indicated to "manage and relieve the burning and itching experienced with various types of dermatoses, including atopic dermatitis, allergic contact dermatitis, and irritant contact dermatitis."[1] It is recommended that the AMHS-based cream be "applied 2 to 3 times daily or as directed by a physician."[1]

RATIONALE FOR CLINICAL USE

Studies evaluating AMHS-based cream include the following:

1) a comparative, 21-day, cumulative, irritation study
2) demonstration of protection against recognized skin allergens and reduced expression of eczematous dermatitis in subjects with known allergic sensitivity
3) evaluation of resolution of allergic contact dermatitis
4) demonstration of reduction in severity of symptoms associated with contact dermatitis
5) results of substantivity testing after handwashing
6) evaluation of protection against lactic acid stinging.

DISCLOSURE: Dr. Del Rosso is a consultant to, speaker for, and performs research for Obagi Medical Products, Arcutis, Allergan, Coria, Galderma, Graceway, Intendis, Medicis, Onset, OrthoNeutrogena, PharmaDerm, Quinnova, Ranbaxy, SkinMedica, Stiefel, Triax, Unilever, and Warner Chilcott. Drs. Bhambri and Michaels identified no conflicts of interest.
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The results of these trials support the role of the AMHS-based cream as the first prescription topical agent proven to provide barrier protection against external allergens and irritants. Importantly, this formulation is unlike other prescription barrier repair creams as its mechanism is not principally through moisturization and replacement of skin lipids. Rather, it has been formulated, in addition to reducing symptoms of eczematous dermatitis, to provide barrier protection against sensitization and/or irritancy induced by external contactants. The barrier protectant properties of the AMHS-based cream support its use primarily in the management of hand dermatitis.

CUMULATIVE IRRITATION STUDY

The AMHS-based cream (Tetrix) was evaluated in normal healthy adults (age range 18–65 years) under both occlusive and semiocclusive patches applied once daily on the upper back (infrascapular region) for 21 days as part of a cumulative irritation study evaluating multiple products.[2] Johnson's Baby Oil (Johnson & Johnson) was used as a negative control. Approximately 24 hours after application, the test patches were removed daily by site personnel and evaluated. A 3+ or greater cutaneous reaction at any time point resulted in termination of further patch applications with the observed score assigned ("carried forward") for the remainder of the study. Cumulative irritation scores were calculated by summing the numerical irritation grades over the 21 days of testing. The evaluable population included 45 subjects.

Results obtained under semi-occlusion demonstrated a *mild rating* with the AMHS-based cream, and the results were lower than the negative control. Although it is not suggested that the AMHS-based cream be used under occlusion, occlusive patch-testing results determined that the AMHS-based cream is "probably mild" with clinical use, indicating evidence of slight potential for very mild cumulative irritation under occlusive conditions.

SKIN BARRIER PROTECTION EFFECTS

A single-center, investigator-blinded, controlled trial was completed in adult subjects (mean age 53.2 years) to determine whether or not the AMHS-based cream could provide barrier protection against nickel sulfate, neomycin, and fragrance mixture in subjects with known sensitivity to these allergens.[3] Of the 35 evaluable subjects, 12, 12, and 11 were allergic to nickel sulfate, neomycin, and fragrance mixture, respectively.

Eligible subjects had four pairs of test sites marked on their upper back. The AMHS-based cream was applied to only one test site in each of the four test-pairs. After the AMHS-based cream dried, the allergen to which the subject was known to be sensitive was applied (dispersed in petrolatum) to both sites within the first three test pairs. The fourth pair served as a control and included the AMHS-based cream on one side and white petrolatum on the contralateral side. All sites were covered with a Finn Chamber. An open test was also completed on the volar forearm (16-cm^2 region) of each subject with the AMHS-based cream applied first followed by the appropriate known allergen for each subject. Signs of delayed-type hypersensitivity were graded according to the North American Contact Dermatitis Group 4-point scale, with assessments made at 6, 24, 48, and 96 hours after initial application of test materials. Paired patches were occluded for 6, 24, and 48 hours. Summary statistics were tabulated for collected variables, and differences were analyzed using paired *t* test or the Wilcoxon test.

A summary of results is as follows:

- The results demonstrated across all tested subjects that a smaller percentage exhibited positive reactions at the test sites where the AMHS-based cream was applied before the allergen as compared to the allergens alone.
- The differences between the test sites were significant at 24 hours with positivity noted in 28.6 percent of sites where AMHS-based cream was applied before the known allergen as compared to 57.1 percent with the allergen alone (p=0.0039).
- The differences between the test sites were significant at 48 hours with positivity noted in 68.6 percent of sites where AMHS-based cream was applied before the known allergen as compared to 80.0 percent with the allergen alone (p=0.0455).
- Overall, at every time point following all durations of test-site occlusion, the proportion of subjects who exhibited positive reactions was lower at the test sites where the AMHS-based cream was applied before the allergen. These results were statistically significant at sites occluded for 24 hours (p=0.0039) and 48 hours (p=0.0455), and in the latter group, at 96 hours (p=0.0143).
- The AMHS-based cream demonstrated skin-barrier-protection properties against nickel sulfate, neomycin, and fragrance mix, three of the most widely reported cutaneous allergens.
- The results of this study, although clinically meaningful, represent somewhat artificially the use of AMHS-based cream. In clinical practice, this agent would be applied two or three times during the day, thus providing the potential for enhanced benefit in clinical practice.

RESOLUTION OF ALLERGIC CONTACT DERMATITIS

An investigator-blinded study was completed in 12 subjects (mean age 52.1 years) to evaluate whether or not the AMHS-based cream impedes resolution of allergic contact dermatitis.[4] All subjects were known to be nickel sensitive. Allergic contact dermatitis was induced in 10 subjects at two sites on the volar forearm by occluding nickel sulfate under a Finn Chamber for 48 hours. Two subjects did not elicit a marked enough delayed-type hypersensitivity reaction and were excluded from the study. All 10 evaluable subjects were scored for signs of local skin reaction (erythema, induration, edema, flaking, weeping, crusting, ulceration) using a 4-point scale. None of the subjects exhibited crusting or ulceration after 48 hours of occluded exposure to nickel sulfate.

After completion of assessments (after removal of the nickel sulfate-impregnated patches at 48 hours), the AMHS-based cream was applied to a single site on each subject twice daily for 10 days. Investigator assessments with scoring of the same signs of local skin reaction were completed after 4, 7, 9, and 11 days at both the AMHS-based cream treated and untreated sites in all subjects.

Study results are summarized as follows:

- The mean reaction scores for each test site at every visit for all parameters indicated that the AMHS-based cream did not impede the resolution of the allergic skin reactions induced by nickel sulfate.
- The AMHS-based cream consistently demonstrated the same or lower severity ratings for the evaluated parameters as compared to the untreated sites, with no statistical differences noted between the scores for both groups.
- Twice daily application of the AMHS-based cream demonstrated lower scores for erythema, induration, and edema from Day 4 through Day 11 (end of study), suggesting that the AMHS-based cream may provide some degree of therapeutic benefit in reducing the signs of the cutaneous allergic reaction as compared to untreated skin.

THERAPEUTIC EFFECTS IN CONTACT DERMATITIS

An open-label, single-center study evaluated subject assessment of itching and burning in patients (aged 49±14 years) with allergic or irritant contact dermatitis treated with the AMHS-based cream twice daily for 14 days versus nontreated sites.[5] Of the 42 evaluable subjects, 21 were nickel sensitive and 21 presented with hand dermatitis. A Visual Analog Scale (VAS), ranging from 0 (none) to 100 (worst possible), was used to rate scores determined by the subjects for itching and burning as the primary efficacy parameter. Included subjects presented with a diagnosis of hand dermatitis or were nickel sensitive. In the hand dermatitis group, subjects had to score associated symptoms of itching and burning with >50 on the VAS scale to enter the study. In the latter group, exposure to nickel for 48 to 96 hours was used to induce allergic contact dermatitis. At least 1+ skin reaction positivity at both forearm sites and grading of itching and burning with >50 on the VAS scale were required for study entry. There were no major differences between the groups in VAS scores at baseline. Subjects scored their perceived VAS scores for itching and burning at each of six visits (Visits 2–7) after the baseline visit (Visit 1). Investigator assessment of signs of dermatitis (e.g., erythema, induration, edema) were also recorded as secondary parameters.

Study results were as follows:

- Overall, subject assessments based on VAS ratings demonstrated that application of the AMHS-based cream decreased itching and burning at all six follow-up visits over the 14-day study.
- Hand-dermatitis sides treated with the AMHS-based cream consistently demonstrated lower VAS scores for itching and burning at each follow-up visit through the end of study as compared to the untreated side. The difference became statistically significant (p=.0185) at Visit 3 (Days 4–5) and remained as such through Visit 7 (Days 14–15).
- For hand-dermatitis sides treated with the AMHS-based cream, the VAS scores for itching and burning were in the range of 65.8 and 66.2 at baseline, respectively. At Visit 7, the VAS scores for itching and burning decreased to 25.8 and 22.0, respectively. On the untreated side, the VAS scores for itching and burning at baseline were 67.4 and 68.8, respectively, and decreased at Visit 7 to 48.7 and 48.1, respectively.
- In subjects with nickel-induced allergic contact dermatitis, sides treated with the AMHS-based cream demonstrated quicker improvements in itching and burning, although the differences did not reach statistical significance. From Visit 4 (Days 6–7) on, the VAS scores for the sides treated with the AMHS-based cream were consistently lower than for the untreated sides.
- Investigator assessments in this study were consistent with another study discussed above which demonstrated that the AMHS-based cream did not impede improvement of the signs of contact dermatitis.

SUBSTANTIVITY TESTING

A bilateral, randomized, double-blind study compared the substantivity of two test articles, AMHS-based cream versus Vaseline Intensive Care® hand cream, in 10 healthy adult subjects with Fitzpatrick Skin Type I–II.[6] The objective of the trial was to evaluate the ability of the test articles to remain on the skin after handwashing. All study procedures were performed on the same day. Prior to application to the hands of study subjects, the test articles were mixed with a fixed concentration of a cosmetic foundation. As this pigment does not penetrate skin, its visibility on the surface of the skin indicates presence of the test article. Premeasured amounts of the test articles were applied to the hands. The hands to which the AMHS-based cream and Vaseline Intensive Care® hand cream were applied were randomized to assure proper blinding of the study, with application completed by a blinded technician. After 15 minutes, a controlled hand wash using a defined routine and designated cleanser was completed by a blinded technician. After completion of washing, the hands were rated for residual presence of pigmentation.

The residual pigmentation four-point assessment scale was graded as none (0), minimal (1), mild (2), moderate (3), and significant (4). There were no adverse reactions reported after application of either test article.

Study results are summarized as follows:

- The assessments in this study demonstrated that the AMHS-based cream provides protection against removal by water, including after washing.
- The mean residual pigmentation score for the hands to which the AMHS-based cream was applied was 3.4, compared to 0 for hands that had the Vaseline Intensive Care® hand cream applied. The residual pigmentation

scores in the AMHS-based cream group ranged from 2 to 4, as compared to the Vaseline Intensive Care® hand cream group, which were all graded as 0.

LACTIC ACID STINGING STUDY

Adult female subjects (*N*=40, mean age 39 years) who experienced a stinging sensation when lactic acid 10% solution was applied to their nasolabial folds were evaluated.[7]

The objectives of the study were to evaluate the ability of the AMHS-based cream to protect against externally contacted noxious stimuli and to determine the duration of protection. Subjects rated the severity of stinging response on a four-point scale. In part one of the study, subjects were tested for the degree of protection provided by AMHS-based cream against lactic acid stinging. Three groups of five subjects (*n*=15) were tested at two specified time points after application of the AMHS-based cream. Each subject received two applications of lactic acid 10% solution, randomized as one to each side of the nose (nasolabial fold) at the designated time interval. After application of AMHS-based cream, Group 1 was tested immediately and after 30 minutes, Group 2 was tested at one hour and two hours, and Group 3 was tested at four hours and six hours. Lactic acid 10% was applied after subjects were equilibrated to room humidity and temperature for 15 minutes, with the technician applying two strokes with a cotton swab to the test area. Subject assessment of stinging and/or burning was rated at 2.5 minutes after application of lactic acid solution. In the second part of the study, an additional 25 female subjects were tested for lactic acid stinging at four and six hours post-application of AMHS-based cream.

Study results are summarized as follows:

- The AMHS-based cream produced a mean decrease in the severity of discomfort (stinging, burning) after application of lactic acid 10% solution to the nasolabial folds (lactic acid stinging test). A protective effect against lactic acid stinging/burning appeared to increase over the first few hours after application of the AMHS-based cream, with protection persisting for at least six hours (last time point measured in study).
- In Part 1 of the study, in Group 1, the mean lactic acid stinging/burning score decreased from a prequalification rating of 1.00 to 0.6 immediately after application of AMHS-based cream, and to 0.2 at 30 minutes after application of AMHS-based cream. In Group 2, the mean score decreased from a prequalification rating of 1.00 to 0.6 at one hour after application of AMHS-based cream, and to 0.0 at two hours after application of AMHS-based cream. In Group 2, the mean score decreased from a prequalification rating of 1.20 to 0.4 at four hours after application of AMHS-based cream, and to 0.25 at six hours after application of AMHS-based cream.
- The data from Part 2 of the study evaluates all 30 subjects who underwent lactic acid stinging testing at four hours and six hours after application of the AMHS-based cream. The Part 2 study analysis demonstrated that the mean lactic acid stinging/burning score decreased from a prequalification rating of 1.43 to 0.87 at four hours after application of AMHS-based cream, and to 0.83 at six hours after application of AMHS-based cream.

SUMMARY

Based on the reviewed studies, the AMHS-based skin barrier protection cream has been shown to:

1) have minimal irritation potential based on cumulative irritation data
2) protect against recognized skin allergens such as nickel sulfate, neomycin, and fragrance mix
3) reduce expression of eczematous dermatitis in subjects with known allergic sensitivity
4) reduce severity of symptoms associated with contact dermatitis
5) not impair improvement of contact dermatitis
6) decrease stinging/burning after exposure to noxious stimuli (lactic acid stinging)
7) exhibit protection against removal by water, including handwashing.

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