Topical Application of 5% Acyclovir and 1% Hydrocortisone Cream (Xerese™) Does Not Cause Phototoxicity in Healthy Volunteers

Larry N. Gever, PharmD and William Wheeler, PhD

Meda Pharmaceuticals, Inc., Somerset, New Jersey

ABSTRACT

Hypothesis: The combination of 5% acyclovir and 1% hydrocortisone cream (AHC, ME 609, Xerese™) is approved for the topical treatment of recurrent herpes labialis. AHC has an absorption spectrum in the UVB region (290–320 mm). A phototoxic material will produce either a wheal-and-flare response immediately after exposure, or erythema and edema 24, 48, or 72 hours later. The objective of this study was to determine whether the administration of AHC when applied to skin that is exposed to sunlight, would cause a phototoxicity reaction.

Materials and Methods: A single-center, double-blind, randomized, vehicle controlled study. Healthy male and female subjects 18–65 years of age with skin types I, II, or III (Fitzpatrick classification) were eligible for inclusion in the study. Following the determination of the minimal erythema dose (MED), 5 test sites measuring 2×2 cm were outlined in a horizontal fashion on the lower aspect of the mid-back region of each subject. A single application of AHC 40 mg and the vehicle were applied in duplicate to designated test sites. All test sites were covered with a semi-occlusive tape for 24 hours. One site served as an irradiated control. After removal of the patches, the test sites were exposed to 20J/cm^2 of long-wave ultraviolet (UVA) 320 to 400 nm plus 0.5 MED of full spectrum solar-stimulated radiation. Test sites were examined for reactions at the end of UV-exposures and at 24, 48, and 72 hours post-exposure. Dermal reactions were graded on a scale of 0 to 4 (0=normal skin, 4=vesicular or blistering reaction). Adverse events (AEs) were assessed.

Results: 30 subjects were analyzed for skin reactions and safety. No subject had a phototoxicity reaction following UVR exposure to the test site. At 24 hours post-exposure, 9/30 subjects developed mild erythema (Grade 1) that was of equal intensity and considered a normal sunburn response to the UVR exposure. No reactions were observed in the remaining 21 subjects. Faint erythema (Grade 1) was still present in some of the exposed test sites in 4/9 subjects at 48 hours post-exposure. The erythema resolved in the remaining 5 subjects. No residual erythema was detectable in any subject at 72 hours post-exposure. There were no AEs and no withdrawals.

Conclusions: Topical application of the combination of 5% acyclovir and 1% hydrocortisone cream and its vehicle were safe and well tolerated and did not exhibit detectable phototoxicity in this study.

INTRODUCTION

- Herpes simplex labialis, or cold sores, are a common recurring infection of the skin due to the herpes simplex virus (HSV). The majority of cases are due to HSV-1.[1,2]
- Seroprevalence of HSV-1 in the United States is 57.7% among patients between the ages of 14–49.[3]
- Antiviral drug therapy is the current standard of care for treatment of recurrent HSV infections.[2]
- In August 2009, the FDA approved a new antiviral/corticosteroid combination therapy acyclovir 5% and hydrocortisone 1% cream (AHC, Xerese™) for the treatment of recurrent HSV infections.[1]
- AHC has an absorption spectrum with absorption in the UVB region (290–320 nm). The present study was performed to evaluate whether AHC, when applied to skin that is exposed to sunlight, could result in a phototoxicity reaction.

OBJECTIVE

- The objective of this study was to determine whether AHC had a potential to cause a phototoxicity reaction

METHODS

Study Design

- Single-center, double-blind, randomized and vehicle controlled study

Study Treatment

- Treatment consisted of application of a single 24 hour patch with 40 mg AHC to 5 test sites

Patients

Inclusion Criteria

- Healthy subjects 18–65 years of age with skin types I, II, or III (Fitzpatrick classification)
  - Type I: Always burns easily, never tans
  - Type II: Always burns easily, tans minimally
  - Type III: Burns moderately, tans gradually

Exclusion Criteria

- History of photosensitivity
- History of recurrent dermatological conditions (eg. psoriasis, atopic eczema, urticaria)
- History of allergy or hypersensitivity to cosmetics, toiletries, or other dermatological products
- Use of anti-inflammatory medications, antihistamines, and/or systemic or topical medications that could interfere with delayed immunologic responses (eg. glucocorticosteroids and immunosuppressants)
- Use of medications which are potentially photosensitizing (eg. sulfonamides, tetracyclines, thiazides, etc.) or any significant medical conditions

Determination of the Minimal Erythema Dose (MED)

- The MED was determined in every subject on the first study day by exposing 6 small (~1/2 inch diameter circle) individual test sites over the lower back to a series of exposures in 25% incremental doses from a solar simulator light source
- The MED was recorded at 20±4 hours later as the smallest exposure required to produce a barely visible erythema

Drug Application and UV Exposures

- After the MED was determined, 5 test sites measuring 2 × 2 cm were outlined in a horizontal fashion on the lower aspect of the mid-back region of each subject
- A single application of AHC and the vehicle were applied in duplicate to designated test sites
- All test sites were covered with a semi-occlusive tape for 24 hours. One site served as the control
- After removal of the patches, the test sites were exposed to 20J/cm^2 of long-wave ultraviolet (UV) 320 to 400 nm plus 0.5 MED of full spectrum solar-stimulated radiation
- Test sites were examined for reactions at the end of UV-exposures and at 24, 48, and 72 hours post-exposure. Dermal reactions were graded on a scale of 0 to 4
  - 0=normal skin
  - 1=minimal visible erythema
  - 2=deeper erythema with clear distinct borders
  - 3=intense erythema and edema (elevated or infiltrated lesion)
  - 4=vesicular or blistering reaction
- Adverse events (AEs) were recorded

Statistical Analysis

- No statistical analysis was performed. Categorical data were presented using counts and percentages and continuous variables were presented using mean, standard deviation, median, minimum, maximum, and numbers of subjects
- All subjects who received at least one application of study drug were included in the safety population and were used for all other data summaries

RESULTS

Study Disposition and Demographics

- Thirty subjects entered and completed the study (**Table 1**)

Table 1. Baseline and Demographic Characteristics (Safety Population)

	All Subjects, N=30
Gender	
Female, n (%)	26 (87)
Race	
Caucasian, n (%)	30 (100)
Fitzpatrick skin type, n (%)	
Type I	10 (33)
Type II	10 (33)
Type III	10 (33)
Mean (SD) age, years	30.7 (9.49)
Mean (SD) weight, kg	70.6 (18.23)

Phototoxicity Analysis

- Following UV-exposure to the 3 designated test sites, no abnormal immediate reactions suggestive of phototoxicity were observed in any of the subjects
- At 24 hours post-exposure, 9/30 subjects developed mild Grade 1 erythema, equivalent to a MED reaction, in all three irradiated test sites (**Table 2**). These reactions were of equal intensity, including the untreated control site, and were interpreted as a "normal" sunburn response to the UV-exposure
- At 48 hours, faint Grade 1 erythema was still present in some of the exposed test sites in 4/9 subjects who developed erythema by 24 hours (**Table 3**). In all 4 subjects, the erythema was present in the test site treated with the vehicle and the untreated, irradiated site. 2/4 exposed subjects also exhibited erythema in the AHC irradiated site. The erythema resolved in the remaining 5 subjects.
- By 72 hours, no residual erythema could be detected in any of the 30 subjects

Table 2. Test Site Evaluations, 24 Hours after Exposure (Safety Population, N=30), n (%)

Grading Scale	AHC+UV	Vehicle +UV	AHC	Vehicle	Untreated +UV
0	21 (70)	21 (70)	30 (100)	30 (100)	21 (70)
1	9 (30)	9 (30)	0	0	9 (30)
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0

Table 3. Test Site Evaluations, 48 Hours after Exposure (Safety Population, N=30), n (%)

Grading Scale	AHC+UV	Vehicle +UV	AHC	Vehicle	Untreated +UV
0	28 (93)	26 (87)	30 (100)	30 (100)	26 (87)
1	2 (7)	4 (13)	0	0	4 (13)
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0

Safety

- No adverse events were reported in any of the subjects exposed to single topical applications of AHC and vehicle
- There were no withdrawals, deaths, or serious adverse events reported

REFERENCES

1. St Pierre SA, Bartlett BL, and Schlosser BJ. Practical management measures for patients with recurrent herpes labialis. *Skin Therapy Lett.* 2009:14(8):1-3.
2. Spruance SL and Kriesel JD. Treatment of herpes simplex labialis. *Herpes.* 2002;9(3):64-69.
3. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA.* 2006;296(8):964-973.

CONCLUSIONS

- **Results of this study demonstrate that AHC and its vehicle do not possess a detectable phototoxicity potential when examined under the conditions of this study and following UV-exposure**
- **No abnormal reactions suggestive of phototoxicity were observed during a 72-hour follow-up period**

This research was funded by Medivir AB.