

Cumulative Irritation Potential Among Metronidazole Gel 1%, Metronidazole Gel 0.75%, and Azelaic Acid Gel 15%

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Topical therapy for rosacea aims to reduce inflammatory lesions and decrease erythema but can carry side effects such as stinging, pruritus, and burning. Metronidazole and azelaic acid gel 15% are US Food and Drug Administration–approved for the treatment of rosacea. The current study was conducted to assess the cumulative irritation potential of 2 formulations of metronidazole—0.75% gel and 1% gel—and azelaic acid gel 15% over 21 days (N=36). Results of this study demonstrated a significantly greater potential for irritation from azelaic acid compared with metronidazole gel 0.75% ($P<.0001$), which had significantly greater potential for irritation compared with metronidazole gel 1% ($P=.0054$). Metronidazole gel 1% had a similar profile to white petrolatum.

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Rosacea is referred to as a multiphasic facial skin disease that is associated with symptoms such as flushing, erythema, papulopustular eruptions, and rhinophyma.¹ It affects individuals worldwide, with an estimated 14 million individuals with rosacea in the United States alone.² Although the cause of rosacea is unknown, several factors have been identified as possible triggers of the disease, including genetic, environmental, vascular, and inflammatory

factors, as well as microorganisms such as *Demodex folliculorum* and *Helicobacter pylori*.³

In a recent survey of 605 individuals with rosacea conducted by the National Rosacea Society, 93% of respondents reported some physical discomfort associated with their condition, most commonly facial burning (72%), facial itching (61%), stinging (52%), swelling (41%), tenderness (40%), tightness (36%), tingling (31%), and prickling sensation (24%).⁴

Metronidazole was the first topical therapy approved for rosacea by the US Food and Drug Administration.⁵ Metronidazole currently is available in a 0.75% cream, 0.75% lotion, 0.75% gel, 1% cream, and 1% gel. Although azelaic acid is available in 2 formulations, a 20% cream and 15% gel, only the 15% gel is indicated for the treatment of rosacea.

Multiple well-controlled trials have reported the efficacy and safety of different preparations of topical metronidazole and azelaic acid.⁶⁻¹⁸ One recent study reported that daily use of metronidazole gel 1% compared with twice-daily use of azelaic acid gel 15% for 15 weeks provided similar efficacy for patients with moderate rosacea.⁷ Moreover, both metronidazole gel 1% and azelaic acid gel 15% had good safety profiles based on the low incidences of adverse events (AEs). This current study reported more patients treated with azelaic acid had moderate to severe stinging and burning compared with patients treated with metronidazole ($P=.002$); however, more patients treated with metronidazole had moderate scaling compared with patients treated with azelaic acid ($P=.045$).⁷ In addition, a randomized trial comparing azelaic acid gel 15% and metronidazole gel 0.75% reported more patients treated with azelaic acid experienced mild to moderate facial skin signs and symptoms than patients

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treated with metronidazole (26% [32/124 patients] vs 7% [9/127 patients], respectively).¹⁸ Few studies have reported the irritation potential of these topical agents. Because the skin of patients with rosacea is hypersensitive to irritants, choosing a treatment option with a lower potential for irritation is prudent. The purpose of this study was to directly compare the cumulative irritation potential of gel formulations (metronidazole and azelaic acid) used in rosacea treatment.

Materials and Methods

This study was conducted as a single-center, active- and negative-controlled, investigator-blinded, intra-individual comparison with randomized applications. The study was conducted according to good clinical practices and local legal requirements. All subjects signed an institutional review board–approved informed consent.

Subjects—The study inclusion criteria called for approximately 35 healthy subjects of any race, at least 18 years old, with Fitzpatrick skin types I to IV. Pregnant and breast-feeding females were excluded from enrollment. Possible interference of study results excluded subjects with a history of atopic dermatitis, eczema, or psoriasis; known allergies to test products; or abnormal pigmentation of the skin at the test areas. Participation in another investigational drug or device study within the last 3 months was not allowed. Washout periods included 1 week for any topical medication; 4 weeks for any topical metronidazole and/or azelaic acid product; 2 weeks for oral corticosteroids, nonsteroidal anti-inflammatory drugs, and salicylic acid greater than 1 g/d; and 3 months for oral metronidazole.

Materials—Subjects received a unique number (subject identifier) at entry into the study corresponding to a randomized product application order. Application sites were designated by 1, 2, 3, and 4 on one side (left or right) of the spine. Each of 4 products (metronidazole gel 0.75%, metronidazole gel 1%, azelaic acid gel 15%, and white petrolatum [control]) was applied to 1 of 4 designated sites. Approximately 0.2 g of each designated product was applied under occlusive conditions to the designated site on the upper back of each subject every 24 hours. The elapsed application time was extended to 72 hours on the weekends. During the 21 days of the study, subjects were instructed to avoid sun exposure, use of any cosmetics to the test sites, upper back exposure to water, and vigorous exercise.

Clinical Assessments—Skin assessments for expected skin reactions, such as erythema, were performed at each application site on the subject's back prior to the initial application of test

Subject Demographics

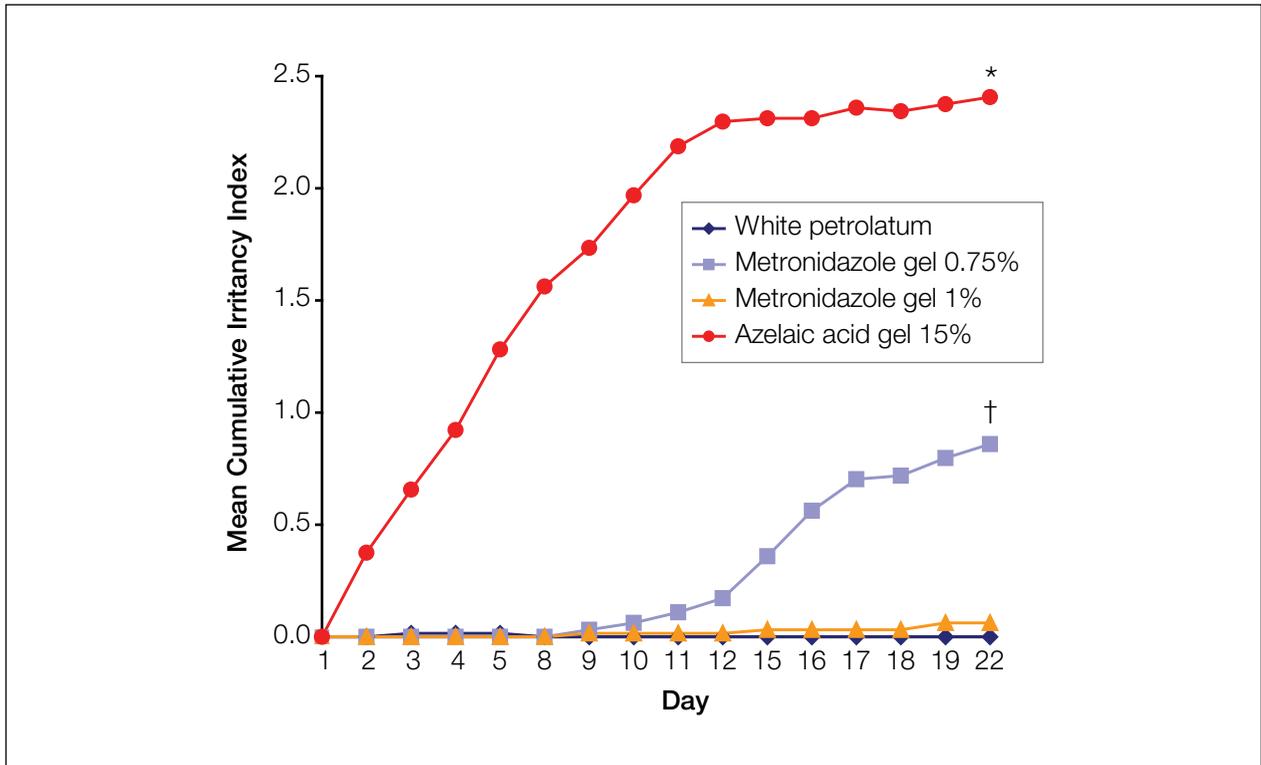
Characteristic	Subjects, n (%) (N=32)
Sex	
Male	7 (21.9)
Female	25 (78.1)
Age, y	
Mean±SD	41.1±11.6
Median	38.5
Range	25–64
Fitzpatrick skin type	
II	16 (50.0)
III	12 (37.5)
IV	4 (12.5)
Race	
White	28 (87.5)
Black	1 (3.1)
Hispanic	3 (6.3)

products. Erythema was graded on a 5-point scale (0=none, 0.5=erythema barely visible, 1=mild erythema, 2=moderate erythema, 3=severe erythema) within 15 minutes of removal of each occlusive patch. Local skin reactions involved the presence of edema, papules, vesiculation, blisters, pustules, hyperpigmentation, weeping/oozing, or spreading of reaction beyond the evaluated test area. Reactions that involved the occlusive patch were evaluated for marked reaction to plaster.

Statistics—A cumulative irritancy index (CII) was calculated for each subject at each treatment by summing the irritation scores for erythema and other local skin reactions and dividing by the number of readings for each subject. An average of the CII was calculated to obtain a mean CII for each test product, then analyzed by analysis of variance, and further classified using the Tukey multiple comparisons procedure.

Results

Subject Demographics—Forty subjects were screened, and 36 subjects enrolled. A total of 32 subjects (88.9%) completed the study. Four subjects (11.1%) discontinued the study for various reasons. One subject was participating in another study,



The mean cumulative irritation index at each visit was calculated from days 1 through 22 for each test product, excluding weekends. Asterisk indicates $P < .0001$ for azelaic acid gel 15% vs metronidazole gel 0.75%, azelaic acid gel 15% vs metronidazole gel 1%, and azelaic acid gel 15% vs white petrolatum; dagger, $P = .0054$ for metronidazole gel 0.75% vs metronidazole gel 1% and $P = .0023$ for metronidazole gel 0.75% vs white petrolatum.

thereby committing a protocol violation, and was terminated. Two subjects had scheduling conflicts, and one subject withdrew consent to participate in the study. The average age of the subjects who completed the study was 41 years. Most subjects were white (87.5%), female (78.1%), and had Fitzpatrick skin type II (50.0%) (Table).

Irritancy Data—The maximum CII score possible was calculated to be 45 per subject per test product. Metronidazole gel 0.75% (CII score, 0.2859) had significantly more irritation potential than white petrolatum and metronidazole gel 1% with scores of 0.0018 ($P = .0023$) and 0.0222 ($P = .0054$), respectively. Azelaic acid gel 15% had the highest CII score of 1.812 and had significantly more irritation potential than white petrolatum and both concentrations of metronidazole ($P < .0001$ for all comparisons). Mean CII scores from days 1 through 22, excluding weekends, are summarized in the Figure for each test product.

Safety Data—A total of 584 skin reactions were observed, with 457 reactions (78.3%) occurring with azelaic acid gel 15%. Metronidazole gel 0.75%, metronidazole gel 1%, and white petrolatum reported fewer erythematous skin reactions with 114 reactions (19.5%), 10 reactions (1.7%), and 3 reactions (0.5%),

respectively. On the last day of the study (day 22), all 32 subjects (100%) experienced erythematous skin reactions with azelaic acid gel 15%. Among these, 19 (59.4%) of the subjects' reactions were severe. In contrast, 16 subjects (50%) had erythematous skin reactions with metronidazole gel 0.75% on day 22 and only 1 subject (3%) had an erythematous skin reaction with metronidazole gel 1%. Of these, only one reaction was severe and it was with metronidazole gel 0.75%. The worst severity in reactions with metronidazole gel 1% was moderate, experienced by only 1 subject (3%) on day 22. Other nonerythematous reactions were infrequent with 10 accounts of blisters, 8 observations of edema, 3 accounts of vesiculation, and 2 observations of weeping/oozing, all of which occurred with azelaic acid gel 15%.

A total of 69 AEs were reported during the course of this study. Both white petrolatum and metronidazole gel 1% were associated with 3% of these AEs (one event of mild erythematous reaction and one event of moderate erythematous reaction, respectively). Metronidazole gel 0.75% was associated with 16 AEs (23%) and the highest percentage of reported AEs were in response to azelaic acid gel 15% with 51 AEs (74%). Most of these AEs were mild or moderate in nature.

Comment

Physical discomfort such as facial burning and itching are major concerns for patients with rosacea. The National Rosacea Society reported that most patients with rosacea experience at least one type of discomfort.⁴ As the condition worsens, it is likely that he/she will seek a therapy with low potential for irritation. The purpose of this study was to compare the cumulative irritation potential of gel formulations of topical rosacea agents (metronidazole and azelaic acid). Although the number of subjects for this study was sufficient (N=36), other minor limitations are apparent in cumulative irritation studies such as this one. For example, other cumulative irritation studies have reported that variations in skin irritation response and irritancy on the backs of patients, not their faces, may potentially limit the validity of the study.¹⁹⁻²¹ This potential for variability is addressed by having all test products applied to the back. This potential limitation is generally accepted instead of using possible irritants on the faces of subjects. The methodology of irritancy assays has been well-established and documented to confirm that cumulative irritation studies are in accordance with good clinical practices.^{22,23}

This study demonstrated that some potential for irritation was present in all test products; however, metronidazole gel 1% was similar to white petrolatum with significantly lower potential for irritation than metronidazole gel 0.75% ($P < .01$). Both metronidazole gels—0.75% and 1%—had lower irritation potential compared with azelaic acid gel 15%, which had significantly more potential for irritation than all other test products, including the control product, white petrolatum ($P < .0001$).

The 1% gel formulation of metronidazole contains hydrosolubilizing agents (HSA-3™). Some features of this vehicle include being highly spreadable, easy to use, cosmetically friendly, ultramild, nondrying, and moisturizing. A 21-day cumulative irritation study was published comparing metronidazole gel 1%, gel vehicle, and sodium lauryl sulfate cream 0.2% (mild positive control) under occlusive conditions.²⁴ The cumulative irritation scores for metronidazole gel 1%, gel vehicle, and sodium lauryl sulfate cream 0.2% were 5.5, 7.0, and 71, respectively. Irritation scores from this study concluded that metronidazole gel 1% and its gel vehicle virtually are nonirritating.²⁴ Although not confirmed, the hydrosolubilizing agents of metronidazole may play a role in the drug's low potential for irritation.

Collectively, results from this study validate results of a previously published cumulative irritation study that reported azelaic acid gel 15% had a greater irritation potential than metronidazole gel 0.75% in a similar design.²¹ Overall, topical

metronidazole formulations, particularly the 1% gel concentration, exhibit low irritation potential and therefore represent an appropriate choice for the treatment of rosacea.

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