Abstract

Background. Systemic and topical antimicrobials are effective in the treatment of inflammatory acne vulgaris; however, widespread use of these agents is becoming increasingly associated with the emergence of resistant pathogens raising concerns about microorganism resistance and highlighting the need for alternative nonantimicrobial agents for the treatment of acne. Nicotinamide gel provides potent antiinflammatory activity without the risk of inducing bacterial resistance.

Methods. In our double-blind investigation, the safety and efficacy of topically applied 4% nicotinamide gel was compared to 1% clindamycin gel for the treatment of moderate inflammatory acne vulgaris. Seventy-six patients were randomly assigned to apply either 4% nicotinamide gel (n = 38) or 1% clindamycin gel (n = 38) twice daily for 8 weeks. Efficacy was evaluated at 4 and 8 weeks using a Physician’s Global Evaluation, Acne Lesion Counts, and an Acne Severity Rating.

Results. After 8 weeks, both treatments produced comparable (P = 0.19) beneficial results in the Physician’s Global Evaluation of Inflammatory Acne; 82% of the patients treated with nicotinamide gel and 68% treated with clindamycin gel were improved. Both treatments produced statistically similar reductions in acne lesions (papules/pustules; -60%, nicotinamide vs. -43%, clindamycin, P = 0.168), and acne severity (-52% nicotinamide group vs. -38% clindamycin group, P = 0.161).

Conclusions. These data demonstrate that 4% nicotinamide gel is of comparable efficacy to 1% clindamycin gel in the treatment of acne vulgaris. Because topical clindamycin, like other antimicrobials, is associated with emergence of resistant microorganisms, nicotinamide gel is a desirable alternative treatment for acne vulgaris.

Systemic and topically applied antimicrobial agents have been widely prescribed for the treatment of inflammatory acne vulgaris for over 30 years. Although these agents generally continue to be effective, their widespread use has also been associated with the emergence of resistant strains of Staphylococi and Propionibacterium. As early as 1976, samples of cutaneous propionibacterium microorganisms taken from over 1000 acne patients were uniformly sensitive to antibiotics. In contrast, 17 years later, 40% of the 468 acne patients studied in England carried Propionibacteri a strains that were resistant to one or more antibiotics. As a result, guidelines were proposed to restrict the use of antimicrobial agents for the treatment of acne. Propionibacteria resistance should be considered as a cause of antimicrobial therapeutic failure.

These observations have spawned renewed interest in the development of alternative therapy for acne providing the therapeutic characteristics of antimicrobial agents without the problem of bacterial resistance. Nicotinamide has potent antiinflammatory properties, and the compound has been used both topically and systemically in a variety of cutaneous inflammatory disorders. The present study was conducted to determine the efficacy and safety of topically applied 4% nicotinamide gel compared to 1% clindamycin gel, in treating inflammatory acne vulgaris.

Materials and Methods

A multicenter, double-blind, randomized, parallel, active-control study was conducted for up to 12 weeks. Data compiled during the first 8 weeks from all centers were analyzed, whereas two of the centers followed patients for a period of 12 weeks. Unfortunately there was an insufficient number of patients studied to allow meaningful analyses in the longer treatment period.

Seventy-six men and women, aged 13 to 35 years, with moderate inflammatory acne vulgaris enrolled in this study. Moderate inflammatory acne was defined by the presence of at least 15 papules and/or pustules on the face. Patients with predominantly comedonal acne were excluded. All concomi-
tant treatments were withdrawn according to the following schedule: topical acne preparations, topical antimicrobial agents, medicated cosmetics, soaps, or shampoos, and radiation therapy, topical corticosteroids, and investigational drugs at least 2 weeks before entry; systemic antimicrobials corticosteroids at least 12 weeks before entry; and oral isorotretinoin at least 2 years before entry. The only concomitant medications permitted were oral contraceptives, if they had been used continuously for at least 3 months before entry and the dosage schedule was not expected to change during the study period. Exclusion criteria included: pregnant or lactating women; patients with more than three nodular lesions on the face; patients with any active skin diseases other than inflammatory acne vulgaris; patients with a history of allergy to study-medications; patients with a previous history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Prior to enrollment, a signed informed consent was obtained.

At the initial qualifying visit, a medical history was obtained and patients were given a dermatologic examination to determine eligibility for study. A lesion count of the entire face was taken, noting the number of papules, pustules, and cysts (baseline only). Additionally, the investigator determined an acne severity grade using Allen and Smith's modification of the Cook et al. procedure (Table 1).

Patients who met all eligibility criteria were assigned to receive either 4% nicotinamide gel or 1% clindamycin phosphate gel in a double-blind, randomized manner. Each patient was instructed to apply the medication to the face twice a day. Patients were supplied with adequate quantities of Ivory® soap and Suave® shampoo to be used exclusively for facial and hair cleansing during the course of the study.

Each patient was required to return for follow-up visits after 4 and 8 weeks of therapy to assess clinical improvement and to elicit information regarding adverse effects. At each follow-up visit, the investigator repeated the Acne Severity Rating and Acne Lesion Count, and also rated the overall improvement of acne compared to pre-treatment examination using a Physician's Global Evaluation of Inflammatory Acne: +3 = much better; +2 = moderately better, +1 = slightly better, 0 = no change, -1 = worse.

Demographic data were analyzed using Student's T-test. The Cochran-Mantel-Haenszel (CMH) chi-square test with ridit-assigned scores was used for analysis of the Physician's Global Evaluation. Percent change from baseline in the Acne Severity Rating and the Acne Lesion Count were analyzed using analysis of covariance. All statistical tests were two-tailed and statistical significance was defined as P ≤ 0.05. Results are expressed as Mean ± SEM.

Table 1. Acne Severity Rating

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Facial skin is clear or a few scattered comedones or papules are visible on close examination.</td>
</tr>
<tr>
<td>2</td>
<td>About one-fourth of face is involved with small papules (6 to 10) and comedones. A few pustules or prominent papules may be present.</td>
</tr>
<tr>
<td>4</td>
<td>About one-half of the face is involved with small papules and comedones. A few pustules or prominent papules are usually present.</td>
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<tr>
<td>6</td>
<td>About three-fourths of the face is involved with papules and/or large open comedones. Numerous pustules are usually present.</td>
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<tr>
<td>8</td>
<td>Practically all of the face is involved with highly inflammatory lesions.</td>
</tr>
</tbody>
</table>

RESULTS

Seventy-six patients, 23 men and 53 women, age 13 to 35 years (mean age 21.3 years) were enrolled in the study. There were no significant demographic differences between the two treatment groups. Seventeen patients failed to complete the study; nine in the nicotinamide treatment group and eight in the clindamycin group. Reasons for premature withdrawal included adverse experience (nicotinamide 2), lost to follow-up (nicotinamide 7, clindamycin 5), non-medical reasons (clindamycin 2) or condition unchanged/worsened from baseline (clindamycin 1). Efficacy results were based on 49 evaluable subjects (nicotinamide 21, clindamycin 28), who participated in at least one evaluation during the treatment period with no protocol violations.

Both clindamycin and nicotinamide treatment was associated with a progressive reduction in acne severity after 4 and 8 weeks of therapy (Fig. 1). At baseline, the mean acne severity rating for the nicotinamide treatment group (4.78 ± 0.19) was nearly identical to the rating for the clindamycin-treated patients (4.84 ± 0.19). After 8 weeks of therapy, the acne severity ratings decreased to 2.48 ± 0.39 in nicotinamide-treated patients (−51.6 ± 7.0%) and to 3.07 ± 0.33 in clindamycin-treated patients (−38.4 ± 6.1%). No significant differences between nicotinamide- and clindamycin-treated patients were evident. Similarly, nicotinamide and clindamycin produced comparable reductions in the number of acne lesions (papules and pustules) after 8 weeks of therapy. The acne lesion count decreased from 27.6 ± 2.1 to 13.5 ± 2.8 (−59.5 ± 9.0%) in the nicotinamide treatment group compared
to a reduction from 29.3 ± 2.0 to 17.0 ± 2.4 (-42.7 ± 7.8%) in the clindamycin treatment group (Fig. 2). Finally, there were no significant differences in the Physician's Global Evaluation of Inflammatory Acne for overall change in acne condition from baseline between the nicotinamide- and clindamycin-treated patients at any time during the study (Fig. 3). At Week 4, 36% of the patients being treated with nicotinamide were rated as either moderately or much better compared to 40% of the clindamycin group. After 8 weeks of treatment, the response rate increased to 86% for nicotinamide compared to 68% for clindamycin (P = 0.19).

The frequency of adverse reactions was similar in both treatment groups (10 nicotinamide-treated patients and nine clindamycin-treated patients) and consisted entirely of local application-site reactions. Localized mild to moderate pruritus and production of excessive oiliness at the application site were reported with topical clindamycin, whereas mild stinging or burning at the site of application was reported with topical nicotinamide. Application site reactions with topical treatment of acne vulgaris have been attributed to vehicle components in previous studies.1,2

DISCUSSION

Nicotinamide is the physiologically active form of niacin and is the source of vitamin B₃ found in a majority of multivitamin products. Nicotinamide serves as a precursor in the synthesis of the coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). As a pharmacologic agent, nicotinamide has been used for its anti-inflammatory properties in such cutaneous disorders as bullous pemphigoid,18 necrobiosis lipoidica,19 and dermatitis herpetiformis.20 In our investigation, we found nicotinamide gel, presumably acting through an anti-inflammatory mechanism of action, to be equivalent in efficacy to topical clindamycin for the treatment of acne vulgaris.

The precise mechanism(s) by which nicotinamide exerts a therapeutic effect in acne vulgaris is unclear. Nicotinamide has been shown to blunt potassium iodide-induced inflammation in human volunteers12 and markedly suppress 12-O-tetradecanoyl-phorbol-13-acetate-induced cutaneous inflammation in mice.13 Nicotinamide may exert an antiinflammatory action through inhibition of mast cell histamine release,14 inhibition of neutrophil chemotaxis and secretion of inflammatory mediators,15 blockade of histamine receptors,16 or suppression of lymphocyte transformation.17 Nicotinamide has other diverse actions such as electron scavenging,23 inhibition of phosphodiesterase activity,24 or increased synthesis of serotonin25 which may also contribute to the pharmacologic activity of this compound. Some or all of these pharmacologic effects of nicotinamide may contribute to the resolution and prevention of inflammatory acne lesions.

After 8 weeks of therapy, 4% nicotinamide and 1% clindamycin gels were equivalent in efficacy for the treatment of inflammatory acne vulgaris as shown by Physician’s Global Evaluation, Acne Lesion Count, and Acne Severity Rating. Unlike topical clindamycin,26,27

Figure 2. Acne Lesion Count: percent reduction in the number of acne lesions (papules and pustules) compared to baseline.

Figure 3. Physicians Global Evaluation of Inflammatory Acne: percent of patients whose acne condition was rated as moderately better or much better.
topical nicotinamide use is not associated with the emergence of resistant strains of microorganisms nor with pseudomembranous colitis. Caution regarding the use of topical and systemic antimicrobial agents, such as clindamycin, erythromycin, and tetracycline, is now commonly advised due to concern about antimicrobial resistance.11

DRUG NAMES

clindamycin phosphate gel 1%: Cleocin
nicotinamide gel: Papulex

REFERENCES

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