SOLUBILIZED BENZOYL PEROXIDE VERSUS BENZOYL PEROXIDE/CLINDAMYCIN IN THE TREATMENT OF MODERATE ACNE

Emil Tanghetti MD,[a] Leon Kircik MD,[b] David Wilson MD,[c] Sunil Dhawan MD[d]

a. Center for Dermatology and Laser Surgery, Sacramento, CA

b. Physicians Skin Care PLLC, Louisville, KY

c. Education and Research Foundation, Lynchburg, VA

d. Center for Dermatology, Cosmetic and Laser Surgery, Fremont, CA

Abstract

Background: Benzoyl peroxide (BPO) is poorly soluble. A solubilized formulation of BPO has been developed to maximize its bioavailability and enhance follicular penetration.

Methods: Patients with acne vulgaris were randomly assigned to receive solubilized BPO 5% gel on one side of the face and a BPO 5%/clindamycin 1% combination product on the contralateral side, twice daily for 4 weeks.

Results: Of 23 patients enrolled, 100% completed the study. Reductions in lesion count with the solubilized BPO gel were at least as great as with BPO/clindamycin—and significantly greater ($P \leq .05$) for noninflammatory lesions at week 1 and inflammatory lesions at week 4. Both regimens were generally well tolerated and patient satisfaction was comparable.

Conclusions: Solubilized BPO 5% gel monotherapy offers significantly greater efficacy, and comparable patient satisfaction, compared with BPO/clindamycin. The early reduction in lesion counts observed with the solubilized BPO gel in the absence of an antibiotic is clinically relevant.

Introduction

Benzoyl peroxide (BPO) can be effective in the treatment of both inflammatory and noninflammatory acne lesions,[1] presumably as a result of its antibacterial and comedolytic activities. It has a key advantage over antibiotics as it is not associated with the development of bacterial resistance.[2] However, BPO is poorly soluble and molecules tend to aggregate together to form crystalline clusters. Commercially available formulations of BPO are generally emulsions of these clusters of which most of the BPO is trapped in the interior of the clusters. As a result, the bioavailability of BPO, and its ability to interact with *Propionibacterium acnes (P acnes)*, is compromised. The size of the clusters can also hinder their passage into hair follicles and, in addition, some commercially successful formulations have vehicles that further inhibit the ability of BPO to penetrate inside hair follicles.

Using a patented technology, 2 novel formulations of solubilized BPO 5% (a gel and a lotion) have now been developed that aim to maximize the bioavailability of BPO and enhance its follicular penetration. In a split-face randomized study evaluating intrafollicular bactericidal activity, the solubilized BPO 5% was shown to achieve a greater reduction in colony forming units of *P acnes* at 8 hours after application than either a prescription generic BPO 5% product or a prescription BPO 5%/antibiotic combination product ($\log_{10}$ reductions of 1.9 solubilized BPO versus 1.7 generic BPO, and 2.5 solubilized BPO versus 1.7 BPO/antibiotic).[3] Furthermore, in a split-face randomized study evaluating skin surface bactericidal activity, the solubilized BPO 5% formulation again achieved a greater reduction in colony forming units of *P acnes* than the BPO 5%/antibiotic combination product ($\log_{10}$ reductions of 2.8 BPO 5% versus 2.4 BPO/antibiotic on the cheeks; and 3.0 BPO 5% versus 2.9 BPO/antibiotic on the forehead).

The solubilized BPO 5% formulations are now available as part of 3-step acne systems (Clenziderm MD™)—the gel formulation for normal to oily skin and the lotion formulation for normal to dry skin. (The 3-step acne system for normal to oily skin also incorporates the use of a proprietary toner and cleanser, both of which contain salicylic acid 2%. The 3-step acne system for normal to dry skin also incorporates the use of a proprietary gentle cream cleanser and a proprietary therapeutic moisturizer containing glycerin and dimethicone.)

The study was designed to compare the clinical efficacy and tolerability of solubilized BPO 5% gel monotherapy (ie, without the other components of the 3-step acne system) with a leading prescription 5% BPO/clindamycin combination product in patients with moderate facial acne vulgaris.

Methods

Study Design

Twenty-three patients enrolled in a 4-week, multicenter, investigator-blinded, randomized, split-face study. Eligible subjects presented with moderate facial acne vulgaris (25-100 noninflammatory lesions, 25-100 inflammatory lesions, up to 2 nodulocystic lesions) and were 11 to 45 years of age. Study subjects were also required to be willing to refrain from using nonstudy acne medications, moisturizers, sunscreens, fragrances, aftershaves, and make-up on the face (oil-free non-

Table 1. Grading scales used for tolerability assessments.

Grade	Stinging/Burning	Erythema	Dryness	Itching
0	*None*: no stinging/ burning	*None*: no erythema present (may be minor discoloration)	*None*: no dryness present	*None*: no itching
1	*Mild*: light warm, tingling sensation, not really bothersome	*Mild*: light pink, noticeable	*Mild*: slight but definite roughness	*Mild*: occasional, slight itching
2	*Moderate*: definite warmth, tingling/stinging sensation that is somewhat bothersome	*Moderate*: pink-red, easily noticeable	*Moderate*: moderate roughness	*Moderate*: constant or intermittent itching that is somewhat bothersome
3	*Severe*: hot tingling/ stinging sensation which is disturbing normal activity	*Severe*: deep or bright red, may be warm to the touch	*Severe*: marked roughness	*Severe*: bothersome itching which is disturbing normal activity

comedogenic make-up, mascara, eyeshadow, and lipstick were allowed). Patients were also required to be willing to avoid excessive exposure to the sun and the use of tanning booths.

Key exclusion criteria included: having undergone a facial cosmetic procedure in the preceding 6 months; an allergy to BPO, clindamycin, lincomycin, salicylic acid, sunscreens or other ingredients in the study products; papulopustular rosacea or other skin diseases on the face (other than acne) that could interfere with study evaluations; facial sunburn at the baseline visit; males with facial hair that could interfere with study evaluations; uncontrolled systemic disease or infection with human immunodeficiency virus; history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis; concurrent facial use of other medicated products; and participation in an investigational study in the preceding 30 days.

The following washout periods were required: 1 week for medicated facial cleansers; 2 weeks for topical alpha-hydroxy acids, antiacne medications, topical retinoids, topical and systemic antibiotics, and topical and systemic steroids; 3 months for estrogens/birth control pills (unless use had been stable for at least 3 months); and 6 months for systemic retinoids.

Treatment Regimen

Patients were assigned to receive treatment with the solubilized BPO 5% gel on 1 side of the face and the BPO 5%/clindamycin 1% combination product (BenzaClin®) on the contralateral side of the face, twice daily for 4 weeks. Determination of facial sides was by random assignment.

Before applying either product, subjects were required to wash the face using a gentle cleanser (provided) and to avoid applying the test products around the lips and eyes. Subjects were also allowed to use a noncomedogenic moisturizer with SPF 15 sunscreen as necessary during the study.

Outcome Measures

The masked investigators evaluated each side of the face weekly to assess the noninflammatory lesion count (open comedones plus closed comedones) and the inflammatory lesion count (papules, pustules, and nodules). Investigators also evaluated the level of erythema and dryness and asked the patients to self-grade any stinging/burning or itching (Table 1). Patients also recorded their level of satisfaction (how the product felt on the skin and the perceived efficacy). Their level of satisfaction was recorded as "excellent", "good", "fair", or "poor".

Statistical Analyses

Between-group differences in the mean percent reduction in lesion count and in the mean scores for stinging/burning, erythema, dryness, and itching were compared using a paired t test or Wilcoxon signed rank test. A P value of $\leq .05$ was considered statistically significant.

Results

Patients

A total of 23 patients were enrolled in the study and all subjects completed the study. The mean age was 21 years and 52% were male. The majority of patients were Caucasian (78%), followed by African American (13%), Asian (4%), and other (4%), and were predominantly of Fitzpatrick skin type 3 (type 3=47%, type 4=21%, type 2=16%, type 5=11%, and type 6=5%). At the baseline visit, patients presented with a mean of 52 noninflammatory lesions and 39 inflammatory lesions.

Figure 1. Mean percent reduction in noninflammatory lesion count.

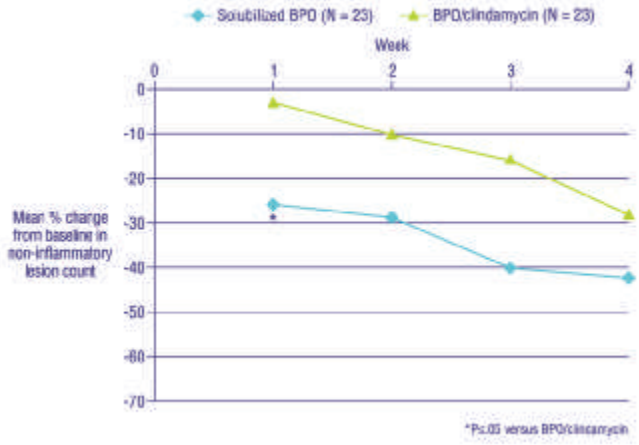


Figure 2. Mean percent reduction in inflammatory lesion count.

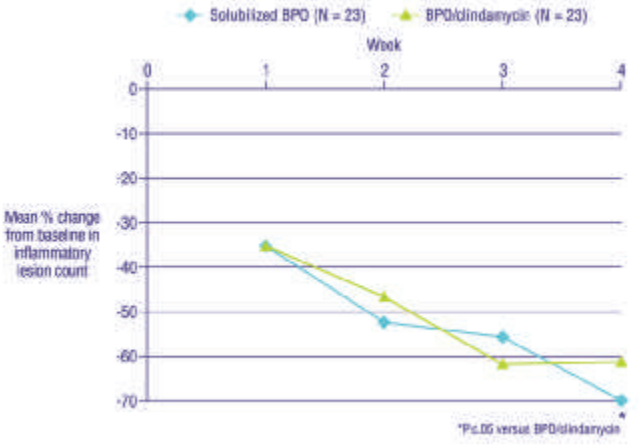


Figure 3. Patient satisfaction (how the products felt on the skin and the perceived efficacy).

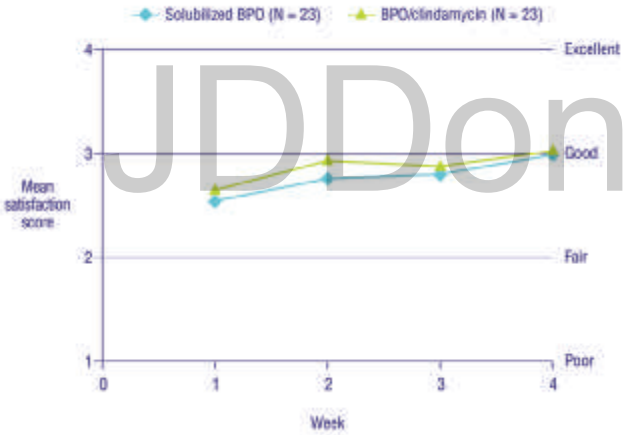
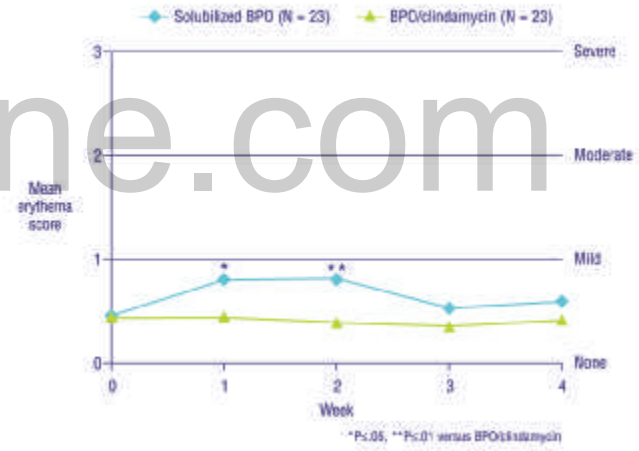


Figure 4. Mean stinging/burning score.



Efficacy

The solubilized BPO 5% gel resulted in a significantly greater ($P \leq .05$) mean percent reduction in lesion count than BPO/clindamycin for noninflammatory lesions at week 1 (Figure 1) and inflammatory lesions at week 4 (Figure 2). At the study endpoint (week 4), the reduction in lesion counts was greater with the solubilized BPO gel than with BPO/clindamycin: a mean of 42% versus 28% for the noninflammatory lesion count, respectively (Figure 1) and 70% versus 61% for the inflammatory lesion count, respectively ($P \leq .05$) (Figure 2).

Patient Satisfaction

Patient satisfaction (how the products felt on the skin and the perceived efficacy) was comparable in both groups (Figure 3). With both regimens, patient satisfaction increased between week 1 and 4.

Tolerability

Mean levels of stinging/burning, erythema, dryness, and itching were less than mild in both groups at all timepoints (Figures 4-7). The mean levels of stinging/burning, erythema, and dryness were transiently higher with the solubilized BPO 5% gel than with BPO/clindamycin at week 1 and 2 ($P \leq .05$), with these differences resolving by week 3. There were no significant differences in itching at any timepoint between the 2 groups.

Discussion

The results of this study demonstrate that the solubilized BPO 5% gel formulation offers an efficacy advantage over BPO/clindamycin, despite the absence of antibiotic in the former. Compared with BPO/clindamycin, the solubilized BPO 5% gel formulation achieved a significantly greater

Figure 5. Mean erythema score.

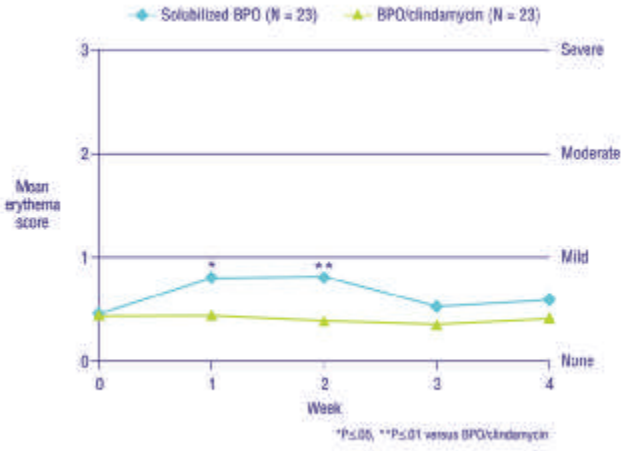


Figure 6. Mean dryness score.

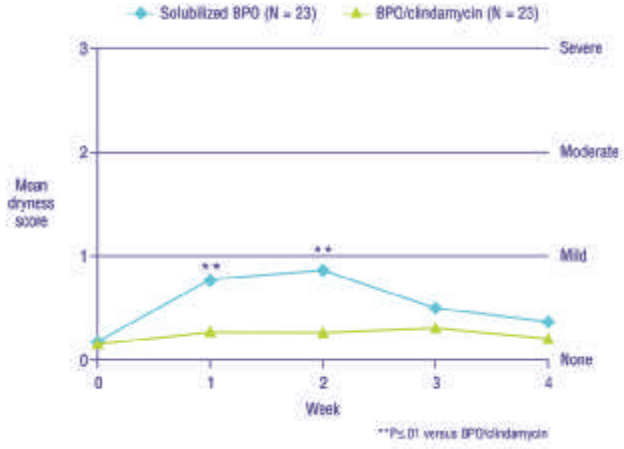
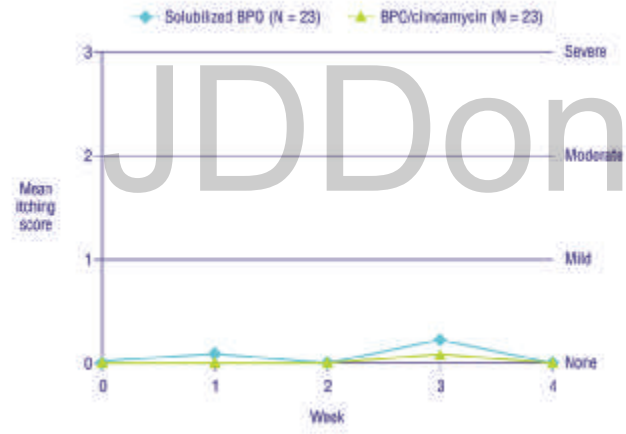


Figure 7. Mean itching score.



mean percent reduction in the noninflammatory lesion count (week 1) and in the inflammatory lesion count (week 4).

Both regimens were generally well tolerated, with comparable levels of patient satisfaction. Although the mean levels of stinging/burning, erythema, and dryness were significantly higher with the solubilized BPO 5% gel than with BPO/clindamycin at weeks 1 and 2, these differences had resolved by week 3 and were likely not clinically significant as they did not reduce mean patient satisfaction scores. Furthermore, they did not result in any premature discontinuations.

The data presented support previous results from an earlier study that compared the efficacy and tolerability of the solubilized BPO 5% gel plus salicylic acid 2% toner (another component of the 3-part acne system) with BPO/clindamycin in 27 patients with mild to moderate facial acne vulgaris.[4] At the endpoint in the earlier study (ie, 2 weeks), the mean reduction in the noninflammatory lesion count was 34% with solubilized BPO gel and 21% with BPO/clindamycin (compared with 29% versus 10%, respectively in the study presented here). Also at week 2, the mean reduction in the inflammatory lesion count was 52% with solubilized BPO gel and 50% with BPO/clindamycin (compared with 52% versus 46% in the study presented here).

These data demonstrate that regimens using the solubilized BPO 5% gel result in reductions in both the noninflammatory and inflammatory lesion count which are at least as great as those achieved with a combination BPO/clindamycin product and significantly greater at some timepoints. The solubilized BPO 5% gel promotes an early reduction in lesion count and this may account for high levels of patient satisfaction. Additional research is now warranted with a larger sample, and extended treatment periods, so that the clinical benefits of the solubilized BPO formulations may be further explored.

Conclusions

Twice-daily monotherapy with the solubilized BPO 5% gel resulted in a significantly greater mean percent reduction in the number of noninflammatory lesions (week 1) and inflammatory lesions (week 4) as well as comparable patient satisfaction when compared with twice-daily therapy with a BPO/clindamycin combination product.

The early reduction in lesion counts observed with the solubilized BPO 5% gel in the absence of an antibiotic is clinically relevant. It is likely that the solubilized BPO formulation facilitates the significant reduction in lesion count during the first week of therapy as a consequence of enhancing the follicular penetration of BPO. Further research will help confirm these findings and evaluate the benefits of long-term treatment.

Disclosures

Dr. Tanghetti is a consultant to Allergan, Stiefel, and Obagi Medical Products Inc. Dr. Kircik has received funding as an

investigator, consultant, or speaker from Abbott Laboratories, Acambis, Allergan Inc, Amgen Inc, Astellas Pharmaceutical Inc, Berlex Laboratories, Biogen Idec, Breckenridge Pharmaceutical Inc, Centocor Inc, Collagenex Pharmaceuticals Inc, Combinatrix, Connetics Corporation, Coria Laboratories Ltd, Dermik Laboratories, The Dow Chemical Company, EDM Serono Inc, Ferndale Laboratories, Galderma Laboratories LP, Genentech Inc, Glaxo-Smith Kline, HealthPoint Ltd, Intendis Inc, 3M, Medicis Pharmaceutical Corporation, NanoBio Corporation, Novartis Pharmaceuticals Corporation, Nucryst Pharamaceuticals Corp, Obagi Medical Products Inc, OrthoNeutrogena, PharmaDerm, QLT Inc, Quatrix, SkinMedica Inc, Stiefel Laboratories Inc, TolerRx Inc, Valeant Pharmaceuticals, and Warner Chilcott. Drs. Wilson and Dhawan report no conflicts. Study supported by Obagi Medical Products Inc.

Data from this study (Figures 1-7) were presented as a poster at the 66th American Academy of Dermatology Annual Meeting, February 1-5, 2008, San Antonio, TX.

References

1. Belknap BS. Treatment of acne with 5% benzoyl peroxide gel or 0.05% retinoic acid cream. *Cutis*. 1979;23:856-859.
2. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49 (suppl):S1-S37.
3. Erianne J, Prince DL, Ramirez J, et al. The pharmacologic science of a novel benzoyl peroxide formulation and the implications for clinical effects. Poster presented at the 25th Anniversary Fall Clinical Dermatology® Conference, October 6-9, 2006, Las Vegas, NV.
4. Wilson DC, Meadows KP, Ramirez J. A comparison of a novel benzoyl peroxide system with a combination benzoyl peroxide and clindamycin product: a 2-week split-face study of effectiveness and tolerability. Poster presented at the 65th annual meeting of the American Academy of Dermatology, February 2-6, 2007, Washington, DC.

ADDRESS FOR CORRESPONDENCE

Emil Tanghetti MD
Center for Dermatology and Laser Surgery
5601 J Street
Sacramento, CA 95819
Phone: 916-454-2155
Fax: 916-454-2156
e-mail: et@mgci.com