# Effect of Topical Benzoyl Peroxide/Clindamycin Versus Topical Clindamycin and Vehicle in the Reduction of *Propionibacterium acnes*

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Propionibacterium acnes is one of the primary factors involved in the pathogenesis of acne vulgaris; proliferation of this bacteria is present in all patients with inflammatory lesions. Combination topical therapy with agents that have different but complementary antimicrobial mechanisms of action has the potential to increase efficacy and to prevent the emergence of resistant organisms. The onset of action and effectiveness of 3 topical preparations (benzoyl peroxide 5%/clindamycin phosphate 1% gel, clindamycin phosphate 1% solution, and vehicle gel) in reducing P acnes were compared in a randomized, open-label, evaluatorblinded, comparative trial involving 60 healthy volunteers who were free of acne but had high levels of facial P acnes. Treatment with benzoyl peroxide 5%/clindamycin phosphate 1% gel significantly (P<.001) reduced P acnes levels by >1  $log_{10}/cm^2$ from baseline (91% inhibition) 24 hours after application. Progressive declines were observed throughout the 2-week study period, with a 3 log<sub>10</sub>/cm<sup>2</sup> reduction (99.9% inhibition) from baseline in P acnes at the end of the 2-week treatment period. In contrast, significant (P<.05) reductions from baseline in P acnes levels following treatment with clindamycin phosphate 1% solution were only observed at the last assessment period (2 weeks), with an average reduction of 0.64  $\log_{10}/cm^2$  (77%) inhibition). Patients receiving vehicle gel had no measurable reductions in P acnes from baseline. These results demonstrate that topical benzoyl peroxide 5%/clindamycin phosphate 1% gel produces rapid and clinically relevant reductions in P acnes greater than those produced by singleagent therapy. This activity is likely responsible for the quick onset of clinical efficacy produced by this combination regimen.

Propionibacterium acnes proliferation, a main factor in the pathogenesis of acne vulgaris, occurs in all patients with inflammatory lesions. As a result, antibiotics are a fundamental component of antiacne therapy.<sup>1-3</sup> Topical antiacne preparations such as benzoyl peroxide and topical antimicrobials exert their therapeutic effect at least partially by either killing *P* acnes or inhibiting the ability of this organism to generate chemotactic factors and proinflammatory molecules.<sup>1-4</sup>

Because no single topical agent is completely effective in the treatment of acne vulgaris, combination therapy using agents that have complementary activity such as a topical retinoid and an antimicrobial agent is a rational treatment approach.<sup>1,5</sup> In addition, combination therapies that have different antimicrobial mechanisms of action have the potential to decrease the emergence of resistant strains of *P* acnes.<sup>5</sup> This is an important issue because oral or topical administration of antibiotics (eg, erythromycin, tetracycline, clindamycin) has been associated with an increase in antibiotic-resistant organisms.<sup>6</sup> In addition, the number of patients carrying resistant organisms has increased in recent years,<sup>7</sup> and antibiotic resistance has been associated with poor therapeutic response.<sup>7.9</sup> Combination therapy also may provide faster onset of effect, and patients who see early improvement may be more likely to adhere to treatment.<sup>3</sup>

The combination of topical benzoyl peroxide 5%/clindamycin phosphate 1% gel (BenzaClin<sup>®</sup>,

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Dermik Laboratories) is a preparation that has demonstrated significant clinical efficacy in the treatment of patients with acne vulgaris and has been shown to be more effective than either agent alone.<sup>10-13</sup> The objective of this study was to compare onset of action and efficacy of 3 topical preparations (benzoyl peroxide 5%/clindamycin phosphate 1% gel, clindamycin phosphate 1% solution [Cleocin T<sup>®</sup>, Pharmacia & Upjohn], and vehicle gel) in the reduction of *P acnes*.

# Methods

This was a randomized, open-label, comparative study. Participants were adult volunteers aged 18 to 50 years who were free of acne but had high P acnes levels, as indicated by a high degree of facial fluorescence under a Wood's lamp. Studying individuals with minimal or no acne is an accepted method for evaluating in vivo antimicrobial effects and has the advantage of avoiding technical difficulties in culturing areas of skin covered with inflammatory lesions. Inclusion in the study required baseline P acnes counts of more than 10,000 colonies/cm<sup>2</sup> (on the forehead) confirmed by bacterial counts obtained using the method of Williamson and Kligman.<sup>14</sup> Women of childbearing age were required to have a negative pregnancy test and to use an acceptable method of contraception for at least 28 days prior to enrollment and throughout the study. Exclusion criteria included past or present history of any significant internal disease (eg, cardiovascular, pulmonary, renal), presence of any acute or chronic skin disorder (eg, acne, psoriasis, eczema), and use of any medications such as a retinoid (within the previous 6 months), or any topical or systemic antibiotic (within the preceding 4 weeks) that interferes with skin-surface counts of P acnes. Patients were asked to avoid using medicated or antimicrobial products (eg, shampoos, soaps, acne preparations) throughout the study. The study was approved by an independent institutional review board, and participants provided written informed consent prior to initiation.

Following baseline testing and evaluation for acceptance, subjects were randomized to receive topical treatment (benzoyl peroxide 5%/clindamycin phosphate 1% gel, clindamycin phosphate 1% solution, or vehicle gel) to the forehead twice daily for 2 weeks. The weekday morning treatment was applied under the supervision of a technician at the testing facility in a standardized manner. Subjects self-applied the study medication once daily at night during the week and self-administered the study medication once in the morning and

once at night on weekends. Fifteen minutes prior to applying study medication, subjects were to wash, rinse, and dry their faces. Approximately 0.3 to 0.4 mL of the study medication was applied in a thin film to the entire forehead area and rubbed in for approximately 30 seconds. Subjects were instructed not to use any alcoholic toners, astringents, medicated solutions, abrasive cloths, or sponges. A bland unmedicated soap was provided for washing, showering, and bathing. Quantitative bacteriologic cultures were obtained from the foreheads of volunteers at baseline, 24 and 72 hours after initial application of study medication, and at the end of weeks 1 and 2, using the method of Williamson and Kligman.<sup>14</sup> One side of the forehead was cleansed thoroughly for 30 seconds with a sterile gauze soaked in 0.1% Triton X-100<sup>™</sup> to remove surface debris and bacteria. One mL of wash solution (0.1% Tween<sup>™</sup> 80 in 0.075M phosphate buffer, pH=7.9) was pipetted into a sterile cylinder held firmly to the skin. The area was scrubbed for one minute and the wash fluid collected. A fresh 1 mL of wash solution was added to the cylinder, the scrub repeated, the wash fluid collected, and added to the fluid collected from the first wash. The collection fluid was diluted in 10-fold steps and cultured anaerobically for 7 days. *P* acnes was identified by colony morphology, by susceptibility to P acnes bacteriophage, and, when indicated, by biochemical testing.

Fifteen patients were selected to undergo fluorescent photography of the face and forehead prior to and immediately after the bacteriologic cultures at baseline, and prior to culture at 24 and 72 hours, and 1 and 2 weeks after the initial dose of study medication. The individuals involved in the handling and culturing of the test samples were blinded as to type of treatment. Paired *t* tests were used to compare net changes in *P* acnes counts ( $\log_{10}/\text{cm}^2$ ) within each group at each time point.

# Results

Fifty-nine of the 60 patients (30 men/30 women) who enrolled in the study completed the protocol. Baseline demographics are summarized in the Table. Most subjects were white, with a mean age of 26 years. Baseline *P* acnes counts were similar among all treatment groups (>6  $\log_{10}/\text{cm}^2$ ). Reduction of *P* acnes in response to treatment is summarized in Figure 1. Subjects treated with benzoyl peroxide 5%/clindamycin phosphate 1% gel had a mean 1.06  $\log_{10}/\text{cm}^2$  (ie, 91% inhibition) reduction of *P* acnes levels from baseline following 24 hours of treatment. This reduction was statistically significant (*P*<.001) from baseline. A progressive and

Demographic	Benzoyl Peroxide 5%/ Clindamycin 1% Gel (n=20)	Clindamycin 1% Solution (n=20)	Vehicle Gel (n=19)
Age			
Mean, y (SD)	26.4 (9.0)	26.6 (9.8)	26.3 (7.1)
Range, y	18–46	19–50	18–38
Sex, n (%)			
Male	10 (50)	10 (50)	9 (47.4)
Female	10 (50)	10 (50)	10 (52.6)
Race, n (%)			
White	15 (75)	15 (75)	15 (78.9)
Black	4 (20)	4 (20)	4 (21.1)
Asian	1 (5)	1 (5)	0
P acnes counts,			
log <sub>10</sub> /cm <sup>2</sup> (SD)	6.2 (0.7)	6.3 (0.5)	6.5 (0.5)

# Baseline Demographics and Propionibacterium acnes Levels (N=59)

statistically significant (P<.001) decrease of *P* acnes was apparent over the 2-week treatment period. An additional 1 log<sub>10</sub>/cm<sup>2</sup> reduction from baseline in *P* acnes (99% inhibition) was apparent one week after treatment and a further 1 log<sub>10</sub>/cm<sup>2</sup> reduction was observed by the end of the second week of treatment (99.9% inhibition). Figure 2 shows the effect of benzoyl peroxide 5%/clindamycin phosphate 1% gel on *P* acnes levels in one subject as assessed by fluorescence photography. This patient's *P* acnes counts were drastically reduced 24 hours after initiation of treatment.

Subjects treated with clindamycin phosphate 1% solution had a 0.16  $\log_{10}/\text{cm}^2$  (31% inhibition) and a 0.43  $\log_{10}/\text{cm}^2$  (63% inhibition) reduction from baseline in *P* acres following 24 and 72 hours of treatment, respectively. However, these reductions were not statistically significant from baseline. Surprisingly, *P* acnes levels were higher than baseline after one week of treatment (Figure 1). Treatment with clindamycin phosphate 1% solution did not produce statistically significant reductions from baseline in *P* acres until the end of the second week of treatment, with a 0.64  $\log_{10}/\text{cm}^2$ reduction (77% inhibition, P<.05) from baseline at this time point. There were no measurable reductions in *P* acnes levels in patients receiving vehicle gel at any time point during the study. All treatments were well tolerated, and there were no reports of adverse reactions during the study.

# Comment

In this study, topical benzoyl peroxide 5%/clindamycin phosphate 1% gel produced rapid and statistically significant reductions in P acnes levels as early as 24 hours after treatment. Patients treated with this combination gel had a greater than  $1 \log_{10}/\text{cm}^2$ reduction from baseline (91% inhibition) in P acnes 24 hours following application. Further reductions were observed during the remainder of the study, with virtual elimination of P acnes (99.9% inhibition) after 2 weeks of treatment. Reductions produced by the combination gel were greater than those observed with clindamycin phosphate 1% solution; clindamycin phosphate 1% solution did not produce significant P acnes reductions from baseline until the end of the second week of therapy, with levels never reaching a  $1 \log_{10}/\text{cm}^2$  reduction.

To our knowledge, this article is the first to report *P* acnes reductions of this magnitude after only 24 hours of treatment. Monotherapy with topical erythromycin has been reported to produce a reduction in total propionibacterial count by less than  $1.5 \log_{10}/\text{cm}^2$ ; however, this reduction followed 6 weeks of therapy.<sup>15</sup> In an open-label study involv-

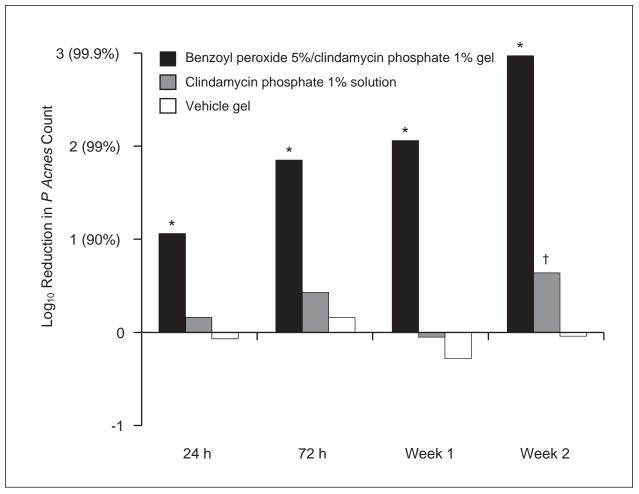
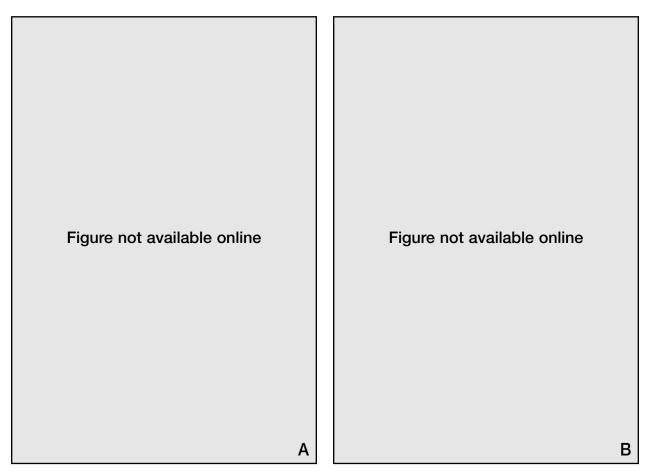


Figure 1. Reductions in *P acnes* among subjects receiving benzoyl peroxide 5%/clindamycin phosphate 1% gel, clindamycin phosphate 1% solution, or vehicle gel. Asterisk indicates *P*<.001 vs baseline; dagger, *P*<.05 vs baseline.

ing 12 subjects, Bojar et al<sup>16</sup> evaluated the effect of 5% benzoyl peroxide treatment on P acnes counts (obtained using the method of Williamson and Kligman) following 2, 4, 9, 14, and 28 days of treatment. *P* acnes counts were reduced by greater than 1.0 and greater than 2.0  $\log_{10}/cm^2$  in 6 and 4 subjects, respectively, following 2 days (48 hours) of treatment (P=.002). In contrast to the present study, baseline P acnes levels were less than  $5 \log_{10}/\text{cm}^2$ , and continued treatment did not result in further reductions of bacterial levels over the 28day (4 week) treatment period. In the present study, patients had baseline levels of *P* acnes greater than  $6 \log_{10}/\mathrm{cm}^2$ , and continued treatment resulted in progressive declines in bacterial levels throughout the study, with a 3  $\log_{10}/cm^2$  reduction observed at the end of the 2-week treatment period. These data suggest that the further reduction in *P* acnes levels observed throughout the present study may be due to the added antimicrobial effects of clindamycin.

While treatment with the combination of benzoyl peroxide 5%/clindamycin phosphate 1% gel significantly reduced P acnes levels, the combination product has the added benefit of inhibiting the emergence of antibiotic-resistant strains of P acnes. In a recent study reported by Leyden and Levy, <sup>13</sup> treatment with the combination product prevented the emergence of resistant *P* acnes, while the number of resistant organisms increased in patients treated with clindamycin only. Baseline levels of clindamycin-resistant *P* acres were minimal (0.6  $\log_{10}/\text{cm}^2$  for the combination group and  $0.9 \log_{10}/\text{cm}^2$  for the clindamycinonly group); however, following 12 weeks of treatment, the number of clindamycin-resistant *P* acnes increased substantially in the clindamycinonly group but remained near baseline in the benzoyl peroxide 5%/clindamycin phosphate 1% gel group.<sup>13</sup> Further increases in resistant organisms were evident in the clindamycin-only group follow-



**Figure 2.** Effect of treatment with benzoyl peroxide 5%/clindamycin phosphate 1% gel in a 27-year-old woman at baseline (A) and 24 hours after initial treatment (B).

ing 16 weeks of therapy, while levels decreased in the combination group.<sup>17</sup> These data indicate that combination therapy is less likely to allow resistant organisms to develop as compared to antibiotic monotherapy.<sup>13</sup>

The results of this study are similar to those reported previously, in which treatment with topical benzoyl peroxide 5%/clindamycin phosphate 1% gel significantly reduced *P* acnes by greater than or equal to 99% (>2  $\log_{10}/\text{cm}^2$ ) from baseline after one week of therapy compared with a 30% to 62% (<1  $\log_{10}/\text{cm}^2$ ) reduction from baseline for 3 different topical clindamycin preparations.<sup>11</sup> In a separate study, benzoyl peroxide 5%/clindamycin phosphate 1% gel produced an approximate 2  $\log_{10}/\text{cm}^2$  reduction (99.0%) in *P* acnes from baseline following 4 weeks of treatment—a reduction significantly greater than that produced by clindamycin alone (85.3% reduction from baseline at 4 weeks).<sup>13</sup>

In the present study, P acnes reductions produced by benzoyl peroxide 5%/clindamycin phosphate 1% gel were both statistically significant and clinically relevant. Leyden and Levy<sup>13</sup> reported a correlation between reductions in total and clindamycin-resistant *P acnes* counts and successful clinical outcomes of treatment with the combination product. In addition, the rapid decline in bacterial concentrations produced by the combination product likely explains the early efficacy observed in clinical trials in which treatment with benzoyl peroxide 5%/clindamycin phosphate 1% gel (compared with vehicle) produced statistically significant reductions in inflammatory lesions after 2 weeks of treatment.<sup>10</sup>

Although the present study was conducted with an open-label design, microbiological evaluations and *P* acnes counts were conducted in a blind fashion without knowledge of treatment applied.

#### Conclusion

The combination of benzoyl peroxide 5%/clindamycin phosphate 1% gel produces rapid reductions in *P* acnes, with activity significantly greater than

that produced by clindamycin phosphate 1% solution alone. This activity is likely the reason for the fast onset of clinical activity.

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