A Combination Benzoyl Peroxide and Clindamycin Topical Gel Compared With Benzoyl Peroxide, Clindamycin Phosphate, and Vehicle in the Treatment of Acne Vulgaris

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A topical gel combining 5% benzoyl peroxide and 1% clindamycin as phosphate was evaluated in a 10-week randomized double-blind trial involving 287 patients with moderate to moderately severe acne. The combination agent demonstrated significantly greater reductions in inflammatory lesions than either of its active constituents (5% benzoyl peroxide and 1% clindamycin) or vehicle when used alone. Significantly greater reductions in comedos and improvements, as measured by both physicians' and patients' global evaluations, were obtained with the combination agent than with clindamycin or vehicle. The reduction in comedos and the global improvements were similar between the combination agent and benzoyl peroxide. The combination agent was well tolerated; the incidence of dry skin was similar to that found with benzoyl peroxide, and other adverse events were similar to that with vehicle. The improved efficacy obtained with combination therapy was accompanied by a safety profile similar to that of either constituent used alone.

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Topical antibiotics and benzoyl peroxide have each demonstrated effectiveness in the treatment of acne vulgaris and are individually accepted therapies for this condition.[1] The effectiveness of topical clindamycin in preventing inflammatory lesions is in part based on its demonstrated in vivo activity against *Propionibacterium acnes*, bacteria that are central to the pathogenesis of acne.[2] In addition, clindamycin has direct anti-inflammatory effects and is more lipophilic than some other antibiotics.[1,3,4] Benzoyl peroxide has demonstrated marked bactericidal activity against *P acnes* by physicochemical means and is highly lipophilic.[5,6] Clinical trials with combinations of benzoyl peroxide and topical antibiotic products containing clindamycin or erythromycin have demonstrated that combination therapy is more effective than either constituent used alone.[7-9] In addition, several studies have demonstrated that the development of antibiotic resistance, increasingly important in the treatment of acne, can be ameliorated by the concomitant use of an antibiotic and benzoyl peroxide.[10-12]

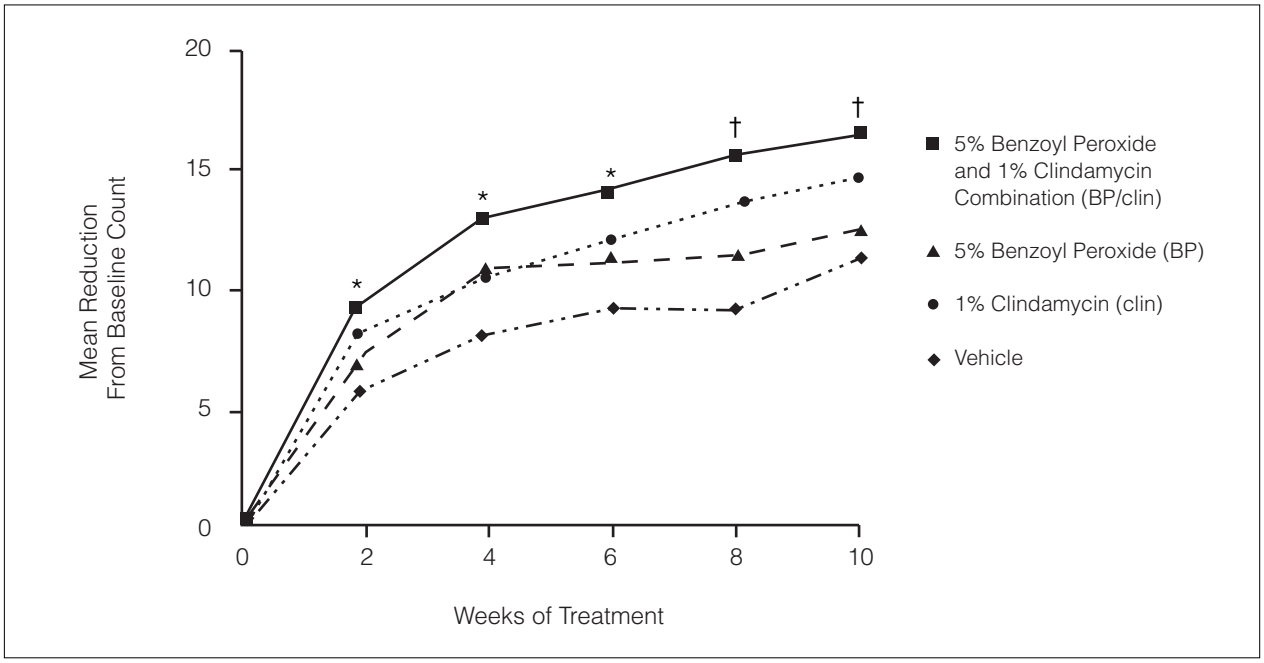

FIGURE 1. Mean reduction from baseline in number of inflammatory lesions (papules and pustules). Significant differences were observed between the BP/clin and vehicle groups from week 2 (*$P \leq .022$) and between the BP/clin and all other groups at weeks 8 and 10 (†$P \leq .034$).

A topical gel formulation has been developed that stably combines 5% benzoyl peroxide and 1% clindamycin as phosphate (BenzaClin™ Topical Gel [clindamycin 1% - benzoyl peroxide 5% gel]) to provide a convenient, multimodal therapy for acne vulgaris. This study compares the efficacy and safety of this combination agent with that of its constituents, benzoyl peroxide, clindamycin, and gel vehicle.

Methods

This randomized, double-blind, parallel-group study was conducted according to the principles of Good Clinical Practice at 5 centers in the United States from September 1996 until January 1997. After giving written informed consent, 287 patients between 13- and 30-years old were enrolled and randomly selected to receive 10 weeks of twice-daily treatment with 5% benzoyl peroxide and 1% clindamycin as phosphate (BP/clin; n=95), 5% benzoyl peroxide (BP; n=95), 1% clindamycin as phosphate (clin; n=49), or vehicle (n=48). All patients had moderate to moderately severe acne (grade 2 or 3 by the Pillsbury classification system[13]), with 10 to 80 inflammatory lesions and 10 to 100 comedos on the face, excluding the nasal skin and labial fold areas. Patients were excluded from the study if they had used topical antibiotics, anti-acne medication, steroids, or retinoids within 2 weeks; systemic antibiotics or steroids within 4 weeks; or oral retinoids within 6 months before the start of the study. Additionally, patients were excluded who had diseases or characteristics (eg, facial hair, pregnancy) that could pose safety issues or affect the study outcome.

Patients were instructed to wash thoroughly with the mild soap supplied and dry with a clean towel before applying blinded study medication. Patients applied treatment twice daily to the forehead, face, and neck and were not to use abrasive cloths, sponges, or skin products other than the supplied moisturizer and sunscreen on the treatment area.

Efficacy and safety were evaluated at baseline and after 2, 4, 6, 8, and 10 weeks of treatment. Measures of efficacy included reduction from baseline at each visit in the numbers of inflammatory lesions (papules and pustules) and comedos and physicians' global evaluations (rated from 5=clear to –5=disease exacerbation). Patients' global evaluations were only measured at week 10 (rated from 3=much better to –3=much worse).

Statistical Analyses—Efficacy analyses included all patients with a posttreatment evaluation. Treatment differences were determined using analysis of covariance (lesion and comedo reductions) and analysis of variance (physicians' global evaluations) including baseline value (as appropriate), study site, treatment, and treatment-by-site interaction as model effects. Significance was determined at $P<.05$ for each comparison in the context of analyses of covariance and variance. Patients' global evaluations were compared using a model for ordered categorical scores, fit by the

logistic procedure, confirmed if needed by Wilcoxon tests. Safety analyses included all randomly selected patients.

Results

Of the 287 patients who were enrolled in the study, 278 had at least one follow-up visit and were included in the efficacy analysis. Treatment groups were well matched with a mean age of 19 years in all groups, acne for 5 to 6 years, and 23 to 27 baseline inflammatory lesions; 46% to 54% of patients were men. Only 9.8% of all enrolled patients did not complete the study, primarily for reasons of noncompliance, and no patients were discontinued for safety reasons.

Efficacy—Throughout the study, the number of inflammatory lesions (papules and pustules) was reduced to a greater extent in patients treated with BP/clin than with any of its constituents (Figure 1). This difference in treatment effect reached statistical significance beginning with week 2 when comparing BP/clin and vehicle ($P \leq .022$) and at weeks 8 and 10 when comparing BP/clin with BP or clin alone ($P \leq .034$). The number of comedos also was greatly reduced with BP/clin, which was statistically significant beginning at week 6 ($P \leq .038$) compared with clin or vehicle. By week 10, mean reductions in comedos were 54.6% with BP/clin, 47.1% with BP, 33.3% with clin, and 34.1% with vehicle.

Physicians' global evaluation scores (from 5=clear to –5=disease exacerbation) were significantly greater for patients using BP/clin than for those using clin or vehicle beginning with week 4 ($P \leq .049$) and week 2 ($P < .009$), respectively. After 10 weeks of treatment, BP/clin and BP resulted in similar physicians' scores (2.9±1.3 and 2.7±1.5, respectively) that were greater than with clin (2.2±1.6) and vehicle (2.1±1.3). At the end of the study, patients' global evaluations (from 3=much better to –3=much worse) were similar to the physicians' evaluations. Patients rated improvement with BP/clin (1.9±1.0) significantly greater than with clin (1.4±1.2, $P = .015$) or vehicle (1.0±1.2, $P < .001$) and similar to that with BP (1.8±1.1). The percentage of patients who considered themselves "much better" was greater in the BP/clin group (34.0%) than in the BP (25.6%), clin (14.6%), or vehicle groups (8.7%).

Tolerability—Approximately half of the patients in each treatment group experienced adverse events, but most events were considered unrelated to treatment and were not unusual for this study population (Table 1). Most of the treatment-related adverse events involved the skin, with dry skin being by far the most frequent. Patients in the BP/clin and BP groups had a greater incidence of dry skin than did those in the clin or vehicle groups. No patient was prematurely discontinued from the study because of an adverse event, but 2 patients in the BP group experienced facial irritation and burning that resulted in changes in treatment (decrease in application frequency to once-daily and a 3-day interruption of treatment).

Comment

In this 10-week study, the combination of 5% benzoyl peroxide and 1% clindamycin in a topical gel formulation was more effective in treating patients with moderate to moderately severe acne than was any of its constituents used alone. Use of the combination agent resulted in statistically greater reductions in inflammatory lesions than benzoyl peroxide or clindamycin alone after 8 weeks of treatment. The combination agent also reduced comedos to a significantly greater extent than clindamycin or vehicle after 6 weeks of treatment. Combination therapy consistently resulted in greater reductions in all lesions than did vehicle and also was shown to be statistically superior to clindamycin and vehicle as evaluated in both physician and patient assessments. These results are consistent with earlier reports of the greater therapeutic efficacy of combinations of topical antibiotic and benzoyl peroxide than with any single constituent.[7-9]

The enhanced activity of combination therapy is likely attributed to a number of factors, including the combined antibacterial and anti-inflammatory actions of benzoyl peroxide and clindamycin.[2,3,5] The increased lipid solubility of the combination and the likelihood that the actions of benzoyl peroxide facilitate the penetration of antibiotic may also enhance clinical efficacy.[14]

Appropriate therapy for the degree of disease severity (grades 2 and 3) seen in this study consists of vigorous topical treatments and/or oral antibiotic therapy.[13] Although effective, oral antibiotics result in systemic exposure to drug and affect gastrointestinal microflora. The better efficacy of this combination agent than its individual components may allow the avoidance of systemic antibiotics in this patient population. Moreover, the new topical gel formulation used in this study has excellent long-term stability when kept under refrigeration, despite the tendency of benzoyl peroxide to degrade antibiotics in formulations of this type.[7]

One of the concerns with the use of antibiotics, whether systemic or topical, is the likelihood of developing resistant organisms. Concomitant use of benzoyl peroxide with topical antibiotics has been shown to prevent the development of resistant bacteria.[11,12] Although not specifically addressed in the present study, the ability of combination therapy to reduce or prevent the emergence of antibacterial

Table 1.

Summary of Adverse Events*

	BP/clin (n=95)	BP (n=95)	Clin (n=49)	Vehicle (n=48)
Patients With ≥1 Adverse Event, %				
Overall adverse events	45	52	51	50
Treatment-related adverse events	23	27	16	19
Treatment-related skin adverse events	22	26	10	10
Patients With Treatment-Related Adverse Events, No. (%)				
Dry skin	20 (21)	21 (22)	2 (4)	4 (8)
Headache	2 (2)	3 (3)	3 (6)	4 (8)
Application site reaction	1 (1)	4 (4)	1 (2)	1 (2)
Pruritus	–	2 (2)	1 (2)	–
Peeling	1 (1)	–	–	–
Rash	–	1 (1)	–	–
Urticaria	–	–	1 (2)	–

*BP/clin indicates 5% benzoyl peroxide and 1% clindamycin as phosphate; BP, 5% benzoyl peroxide; clin, 1% clindamycin as phosphate.

resistance in earlier studies, suggests that this benzoyl peroxide/clindamycin combination may provide an important new treatment alternative for patients with acne vulgaris.

The combination agent had a tolerability profile comparable with that of benzoyl peroxide alone, with the major treatment-related side effect for both medications being dry skin. There were no great differences between treatments in local irritant effects, but the slightly higher incidence of dry skin and other side effects involving skin with benzoyl peroxide alone suggests that the addition of clindamycin may moderate the irritating effects of the benzoyl peroxide gel. With the exception of dry skin, the frequency and type of the few other treatment-related events were similar between the combination agent and vehicle. All together, the data indicate that the combination agent is at least as tolerable as the well-documented benzoyl peroxide gel.[7,9,15]

In conclusion, the combination topical gel formulation containing 5% benzoyl peroxide and 1% clindamycin was more effective in the treatment of acne vulgaris than either of its active constituents used alone, with improvements seen as early as week 2 of treatment. Particular benefit was seen in the reduction of inflammatory lesions. The tolerability profile of the combination agent was at least as good as that of benzoyl peroxide, indicating that the greater efficacy was not at the expense of tolerability.

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