# Comparing 2.5%, 5%, and 10% Benzoyl Peroxide on Inflammatory Acne Vulgaris

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*ABSTRACT: A 2.5% formulation of benzoyl peroxide was compared with its vehicle, and with a 5% and a 10% proprietary benzoyl peroxide gel preparation in three double-blind studies involving 153 patients with mild to moderately severe acne vulgaris. The 2.5% benzoyl peroxide formulation was more effective than its vehicle and equivalent to the 5% and 10% concentrations in reducing the number of inflammatory lesions (papules and pustules). Desquamation, erythema, and symptoms of burning with the 2.5% gel were less frequent than with the 10% preparation but equivalent to the 5% gel. The 2.5% formulation also significantly reduced Propionibacterium acnes and the percentage of free fatty acids in the surface lipids after 2 weeks of topical application.*

Benzoyl peroxide, in concentrations of 5%, 10%, and 20%, has been used effectively in the treatment of acne for more than 20 years.[1-5] This compound has been shown to suppress *Propionibacterium acnes in vivo*, the probable basis for its therapeutic effect.[6] With such concentrations, side effects such as erythema, desquamation, and burning, itching, or stinging are fairly common. This paper describes clinical trials of a 2.5% benzoyl peroxide gel, which was compared with 5% and 10% benzoyl peroxide gels in groups of patients with inflammatory acne vulgaris. Antibacterial and lipid studies were also performed on the 2.5% benzoyl peroxide formulation.

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## Subjects, Materials, and Methods

### *Clinical Studies*

The same methods were used to conduct three double-blind studies. After giving informed consent, subjects with mild to moderately severe inflammatory acne vulgaris of the face (minimum of 10 inflammatory lesions) were assigned to one of the three treatment groups. A total of 153 subjects, 74 men and 79 women (average age of 20 years), participated in the three studies. In the first, 25 subjects used 2.5% benzoyl peroxide gel and 25, the gel vehicle for this formulation. In the second, 26 used the 2.5 gel and 27, a 5% gel. The third study consisted of 25 subjects who used the 2.5% gel and 25, a 10% benzoyl peroxide gel. The subjects received no medications for any reasons during the 4-week period prior to the start of the study.

The study participants were instructed to wash daily with a non-medicated soap, rinse, and dry with a clean towel before applying the study medication to the face twice daily (morning and evening) for 8 weeks. Subjects were examined before treatment for baseline determinations and at weeks 2, 4, 6, and 8 after the start of treatment. At each visit, the number of facial inflammatory lesions (papules and pustules) was recorded. In addition, the frequency and severity of side effects such as erythema, peeling, and burning were noted. A global assessment of improvement was also made by the investigator at each visit, according to the following criteria: "excellent," greater than 75% improvement; "good," about 50% improvement; "fair," about 25% improvement; and "poor," little or no improvement.

### Antibacterial and Lipid Studies

Ten subjects who had a *P. acnes* count of 100,000 colonies per $cm^2$ or greater on the face were selected for this study. A score of 3 or greater on the follicular porphyrin fluorescence scale was also required for admission. The density of *P. acnes*, the degree of porphyrin fluorescence, and the ratio of free fatty acids to triglycerides found in lipid samples were determined before and after 7 and 14 days of twice-daily applications of the 2.5% benzoyl peroxide formulation to the face. All applications were made by laboratory technicians.

At each sample day (0, 7, 14), the skin was prepared by wiping the surface of the forehead for 30 seconds with a piece of gauze saturated with 0.1% Triton X-100 (Rohm and Haas, Philadelphia, PA), followed by a distilled water rinse

TABLE 1. Comparison of Effects of 2.5% Benzoyl Peroxide and Vehicle

| Week | 2.5% Benzoyl Peroxide | | | Vehicle | | | P Value† for Average Treatment Difference |
|---|---|---|---|---|---|---|---|
| | Number of Subjects | Mean Number of Lesions* | Mean % Reduction | Number of Subjects | Mean Number of Lesions* | Mean % Reduction | |
| 0 | 25 | 13.6 | — | 25 | 13.7 | — | 0.91‡ |
| 2 | 25 | 10.8 | 20.4% | 25 | 13.8 | −2.7% | <0.01 |
| 4 | 24 | 9.3 | 31.4% | 25 | 13.0 | 2.8% | 0.02 |
| 6 | 25 | 7.5 | 44.1% | 22 | 13.1 | 3.4% | <0.01 |
| 8 | 25 | 6.8 | 50.9% | 25 | 11.2 | 17.6% | 0.01 |

* Papules and pustules.
† By *t*-test.
‡ Difference in baseline counts.

and a 30-second wipe with hexane. This procedure removed environmental contaminants, desquamating cells, and surface bacteria and lipids. Two areas were protected by plastic weighing boats with several perforations to allow evaporation of sweat. After 1 hour, the site was sampled by the detergent scrub technique of Williamson and Kligman.[9] A sterile glass cylinder with an internal area of 3.8 $cm^2$ was placed over the site. One ml of 0.1% Triton X-100 in 0.075% phosphate buffer (pH 7.9) was added and the surface scrubbed with a blunt Teflon (Arthur H. Thomas, Philadelphia, PA) spatula for one minute. This procedure was repeated, and the two samples were pooled. Subsequently, tenfold dilutions were made in 0.5% buffered Triton X-100; the samples were dropplated on brain heart agar with 0.1% Tween 80 (Atlas Chemical, Wilmington, DE) and incubated anaerobically for 7 days in a Gas Pak (Arthur H. Thomas, Philadelphia, PA) jar system.

*P. acnes* was identified by colony morphology, by susceptibility to *P. acnes* bacteriophage, and, when indicated, by biochemical testing.[10,11]

At the other site on the forehead, lipid samples were collected by putting 2 ml of hexane-containing methyl nervonate, as an internal standard, in the glass cup, as above. The site was scrubbed for 30 seconds with a blunted Teflon policeman. The solution was taken up on a Pasteur pipette and passed through a 0.45-millipore filter to remove skin debris and bacteria. It was then placed in Teflon-capped glass screwtop vials. The vials were uncapped, dried overnight in a vacuum at 40 C, then capped and stored at 40 C until lipid thin-layer chromatography was done by the method of Downing.[12]

Each subject was examined under Wood's light for porphyrin fluorescence prior to washing and obtaining samples.[8] The intensity of fluorescence was graded on a 0 to 6 scale with 0 = none, 1 to 2 = mild fluorescence, 3 to 4 = moderate, and 5 to 6 = heavy fluorescence.

### Statistical Methods

Fisher's exact test[13] was used to compare treatment groups with respect to side effects at each visit during the treatment period. A group *t*-test[14] was used to compare treatment groups with regard to the reduction in number of papules and pustules from baseline. A paired *t*-test[14] was used to analyze changes from baseline counts within treatment groups. The Wilcoxon rank-sum test[14] was used to analyze changes estimated by global ratings.

## Results

Results on efficacy and side effect data are presented separately for each study. No subject was obliged to drop out of any study because of adverse effects.

### Study 1: 2.5% Benzoyl Peroxide Versus Vehicle

The 2.5% benzoyl peroxide was more effective than the vehicle in reducing the number of inflammatory lesions (papules and pustules) at all follow-up visits (Table 1).

The 2.5% benzoyl peroxide was also significantly more effective than the vehicle in global ratings at all evaluations. Mild peeling, burning, and itching were

TABLE 2. Comparison of Effect of 2.5% and 5.0% Benzoyl Peroxide Gel

| Week | 2.5% Benzoyl Peroxide | | | 5% Benzoyl Peroxide | | | P Value† for Average Treatment Difference |
|---|---|---|---|---|---|---|---|
| | Number of Subjects | Mean Number of Lesions* | Mean % Reduction | Number of Subjects | Mean Number of Lesions | Mean % Reduction | |
| 0 | 26 | 21.3 | — | 27 | 19.4 | — | 0.47‡ |
| 2 | 26 | 14.8 | 32.2% | 27 | 13.5 | 30.6% | 0.75 |
| 4 | 25 | 13.3 | 40.3% | 27 | 12.9 | 35.1% | 0.51 |
| 6 | 26 | 10.0 | 54.3% | 25 | 10.6 | 47.2% | 0.41 |
| 8 | 26 | 9.6 | 55.9% | 25 | 7.8 | 57.7% | 0.94 |

* Papules and pustules.
† By *t*-test.
‡ Difference in baseline counts.

TABLE 3. *Comparison of Effects of 2.5% and 10% Benzoyl Peroxide Gel*

| Week | 2.5% Benzoyl Peroxide | | | 10% Benzoyl Peroxide | | | P Value† for Average Treatment Difference |
|---|---|---|---|---|---|---|---|
| | Number of Subjects | Mean Number of Lesions* | Mean % Reduction | Number of Subjects | Mean Number of Lesions | Mean % Reduction | |
| 0 | 25 | 19.7 | — | 24 | 23.7 | — | .17‡ |
| 2 | 25 | 16.1 | 18.3% | 25 | 19.0 | 19.8% | .66 |
| 4 | 24 | 12.8 | 35.0% | 24 | 14.9 | 37.1% | .47 |
| 6 | 24 | 10.9 | 44.7% | 23 | 14.5 | 38.8% | .75 |
| 8 | 24 | 10.5 | 46.7% | 24 | 13.2 | 44.7% | .57 |

* Papules and pustules.
† By *t*-test.
‡ Difference in baseline counts.

more frequent in the benzoyl peroxide group than in the vehicle group, but only statistically significantly so for peeling at week 8. There was no significant difference in the incidence of erythema, although 2.5% benzoyl peroxide more often induced erythema at week 2.

*Study 2: 2.5% Versus 5.0% Benzoyl Peroxide*

No significant difference in efficacy between the 2.5% and the 5.0% benzoyl peroxide formulations was noted. In both groups, a significant reduction in papules and pustules was observed at 2, 4, 6, and 8 weeks (Table 2). The global ratings confirmed the lack of significant difference in efficacy between the 2.5% and 5.0% gel formulations. There was no significant difference between the two preparations in regard to burning, peeling, or erythema.

*Study 3: 2.5% Versus 10% Benzoyl Peroxide*

Both 2.5% and 10% benzoyl peroxide gels reduced the number of papules and pustules from baseline counts, but there was no statistically significant difference between the two groups (Table 3). Statistical evaluation of the investigator's global response ratings also indicated that there was no significant difference between the efficacy of 2.5% and 10% benzoyl peroxide.

There was a statistically significant difference in the frequency and severity of burning, erythema, and peeling among subjects who used 10% benzoyl peroxide than among those who used the 2.5% concentration at all follow-up visits (Table 4).

*Bacteriology and Free Fatty Acids*

A marked reduction in the quantity of *P. acnes* was observed after 1 week (Table 5). The intensity of follicular porphyrin fluorescence was also reduced by 1 week and markedly suppressed by 2 weeks. There was also a significant reduction in the ratio of free fatty acids to triglycerides.

## Discussion

The 2.5% benzoyl peroxide formulation was significantly more effective than its vehicle in reducing the number of papules and pustules and was comparable to the 10% benzoyl peroxide by lesion counts. By the same measurement, there were no differences between the 2.5% gel and the 5% benzoyl peroxide gel; both were clinically effective. The incidence of irritation was lower with 2.5% than with 10% benzoyl peroxide. It should be pointed out that in two of these clinical studies there would need to have been much larger patient groups to assure "statistical power" for differences between treatments. The differences between the 2.5% benzoyl peroxide and its vehicle is not a question. A clear significant difference between these two exists. When the 2.5% versus 5% and 2.5% versus 10% studies were reviewed for "statistical power," it is evident that, with the number of subjects involved, the power of the test was not high enough to assure a difference that was statistically significant. However, we feel these studies are clinically significant and present important information for clinicians and those working in dermatopharmacology.

Also, these studies do not represent a titration of percent concentration of drug in the same vehicle. The 2.5% formulation vehicle was different from those of

TABLE 4. *Frequency and Severity of Burning, Erythema, and Peeling* (Total Number of Reports for 8 Weeks)*

| 2.5% Benzoyl Peroxide Gel | | | 10% Benzoyl Peroxide Gel | | |
|---|---|---|---|---|---|
| | Mild | Moderate | | Mild | Moderate |
| Burning | 20 | 1 | Burning | 57 | 20 |
| Erythema | 22 | 4 | Erythema | 51 | 30 |
| Peeling | 50 | 9 | Peeling | 36 | 55 |

* Possibly or probably related to drug.

TABLE 5. *Effect of Topical Application of 2.5% Benzoyl Peroxide Gel on Quantitative P. acnes Counts, Follicular Porphyrin Fluorescence and Free Fatty Acids in Skin Surface Lipids*

| Subject Number | *P. acnes* (log/cm²) | | | Follicular Porphyrin Fluorescence (Grades 0–6) | | | Free Fatty Acids/Triglycerides | | |
|---|---|---|---|---|---|---|---|---|---|
| | Week 0 | Week 1 | Week 2 | Week 0 | Week 1 | Week 2 | Week 0 | Week 1 | Week 2 |
| 1 | 5.8285 | 4.9254 | 4.4694 | 6 | 4 | 2 | 0.47 | 0.16 | 0.14 |
| 2 | 6.2775 | 4.3647 | 3.6455 | 6 | 5 | 3 | 0.84 | 0.73 | 0.66 |
| 3 | 5.2775 | 3.7547 | 3.6455 | 6 | 6 | 4 | 0.38 | 0.16 | 0.14 |
| 4 | 6.6455 | 4.0223 | 4.4994 | 5 | 4 | 2 | 0.22 | 0.19 | 0.11 |
| 5 | 6.1015 | 5.5538 | 4.0223 | 4 | 3 | 2 | 1.77 | 1.12 | 0.86 |
| 6 | 5.6243 | 3.1684 | 3.4025 | 4 | 4 | 2 | 0.93 | 0.86 | 0.55 |
| 7 | 6.7383 | 5.6657 | 5.6021 | 5 | 3 | 1 | 1.25 | 1.19 | 0.89 |
| 8 | 6.3647 | 4.0223 | 3.7383 | 6 | 4 | 3 | 0.22 | 0.16 | 0.14 |
| 9 | 6.4372 | 5.7383 | 5.6455 | 5 | 3 | 2 | 1.05 | 0.99 | 0.60 |
| 10 | 5.7035 | 4.6021 | 3.1684 | 6 | 4 | 2 | 0.19 | 0.19 | 0.10 |
| Mean | 6.083 | 4.504 | 4.108 | 5.30 | 4.00 | 2.30 | 0.732 | 0.575 | 0.419 |
| *p value* | — | <0.001 | <0.001 | — | <0.01 | <0.001 | — | <0.02 | <0.01 |

the 5% and 10% formulations, but we think it important that we saw these results with percent concentrations of drug that were one-fourth to one-half less than the highest concentration.

The laboratory results from the in vivo study of *P. acnes* showed the 2.5% benzoyl peroxide gel reduced the anerobic population by 97% after twice-daily treatments for 1 week and by 99% after 2 weeks. This outcome is in agreement with previous work using a different 2.5% benzoyl peroxide formulation.[15]

Regarding the clinical changes of peeling and erythema and the symptoms of burning, there were no differences between 2.5% versus 5%, but differences did exist between the 2.5% and its vehicle and the 2.5% and 10% formulations. With this in mind, the lower concentration of benzoyl peroxide should be useful for treating patients with easily irritated skin. Also, in combination topical therapy with comedolytic agents, 2.5% benzoyl peroxide might lessen the expected degree of irritation.

## Drug Names

2.5% benzoyl peroxide: Clear by Design
5.0% benzoyl peroxide: Desquam X-5
10.0% benzoyl peroxide: Desquam X-10

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