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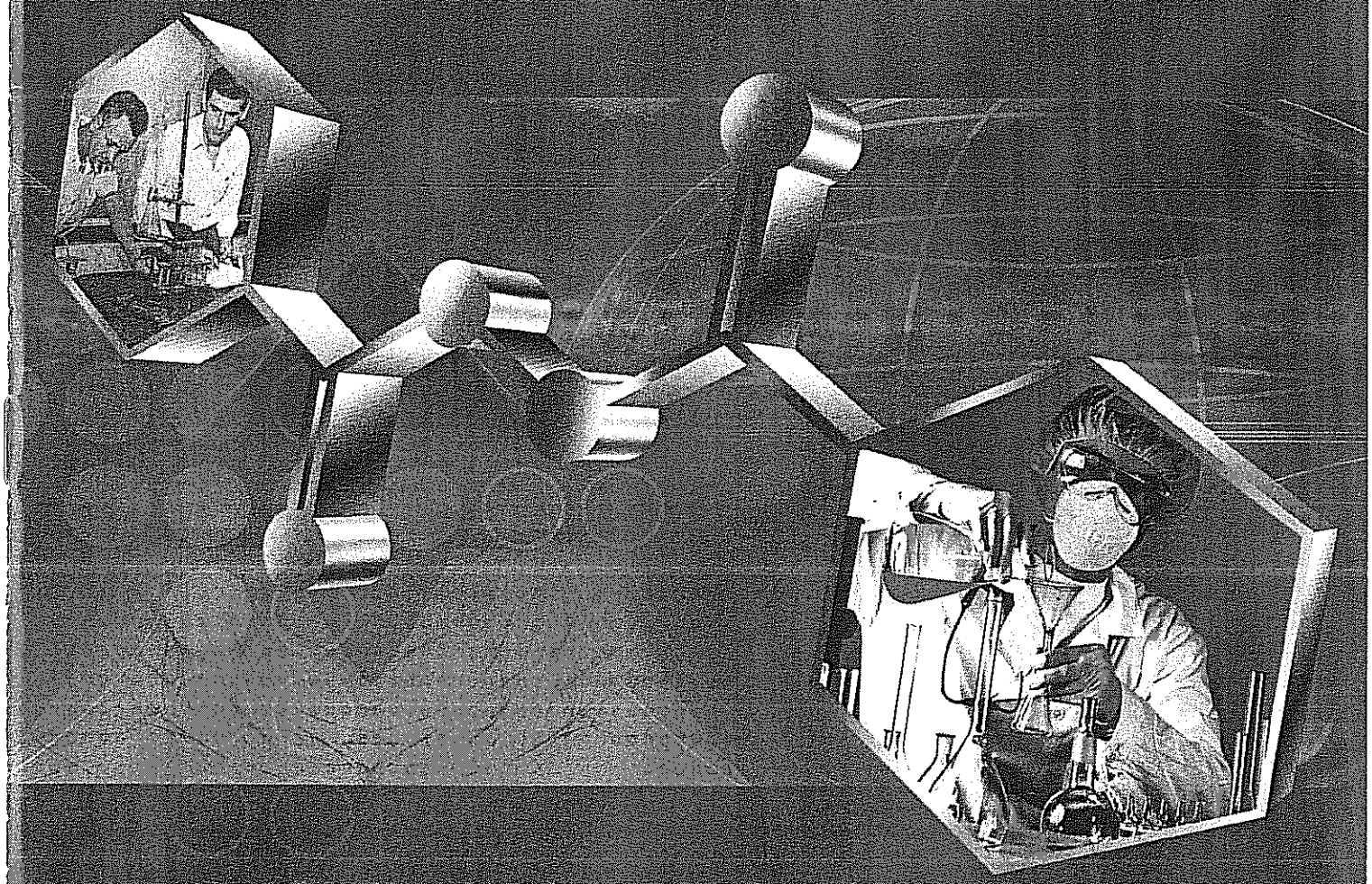

New Perspectives on Benzoyl Peroxide Use in Inflammatory and Comedonal Acne Treatment

Introduction

Emil Tanghetti, MD

Benzoyl peroxide (BPO), an organic peroxide derived from a coal tar by-product, was first used in dermatology early in the 20th century for wound healing and antisepsis.[1] Its earliest use as an acne treatment was by Pace[2] and it was combined with precipitated sulfur in an oil-in-water emulsion. In his 1965 study of 286 patients who also were being treated with oral tetracycline, he noted prompt suppression of inflammatory acne lesions.[2] Since then, BPO has become the most widely used topical acne treatment with proven antibacterial, keratolytic, comedolytic, and anti-inflammatory activity.[3-5] There are more than 100 BPO products available in the United States in both over-the-counter and prescription formulations.

So why reexamine this time-tested drug? Since its earliest uses, many formulation milestones have been achieved, resulting in an array of BPO products in novel formulations that have greatly reduced some of its drawbacks, such as instability in formulation and skin irritation. The history of modern BPO began in 1970 with the development of a formulation that was stable in storage. It was an important improvement over previous formulations, which required mixing of the BPO and base formulation prior to usage.[6] In 1970, Young[7] developed a composition of extremely fine BPO particles in a single-phase aqueous alcohol gel vehicle. It was an improvement over earlier oil-in-water emulsions because it contained no lipids, which may inhibit the antiseptic and keratolytic activity of the BPO. In 1977, Fulton[8] further improved stability during storage by adding glycerol to inhibit decomposition. The development of a delivery vehicle comprising BPO-containing porous polymeric beads provides controlled release. This vehicle also had greater mechanical stability, permitting the vehicle to be handled under more severe conditions without damage.[9] Most recently, a patent was awarded in 1990 for a gel vehicle that contained dimethyl isosorbide, which precipitates BPO as fine crystals to minimize skin contact of BPO particles, thus reducing contact time and irritation.[10] These advances in formulation science led to the widespread adoption of BPO as either monotherapy or in combination with an antibiotic or retinoid to treat both inflammatory and noninflammatory acne.

The completion of *Propionibacterium acnes* genome sequencing has shown that *P acnes* frequently exists in bacterial communities called *biofilms* that adhere to surfaces, such as the pilosebaceous lining.[11,12] Some of the bacterial populations that are more difficult to eradicate have been shown to form biofilms that are not easy to penetrate because of their extracellular polysaccharide lining, which can delay the delivery of antimicrobial agents. This new understanding of *P acnes* is likely to increase the use of BPO, which acts by generating oxygen free radicals that are capable of penetrating the keratin and lipid components of comedones as well as the bacterial biofilm and may make the resident bacteria more susceptible to topical antibiotics.[13]

The increasing incidence of bacterial resistance to the antibiotics currently used in acne management has led to a reexamination of all drugs used in its treatment. Although BPO is bactericidal, *P acnes* still is sensitive to its effects.[14] Current guidelines for acne management recommend that BPO be added to antibiotic regimens to help maintain bacterial sensitivity.[14,15] The use of BPO in combination with an oral or topical antibiotic currently is the standard of care, and the development of fixed combinations of BPO and a topical antibiotic has been driven by this practice recommendation.

The main reason for treatment failure in acne is poor compliance.[16] Fixed combinations of BPO and topical antibiotics may increase treatment success in acne management by simplifying the regimen, thereby improving patient compliance.[17,18] Compliance also is a function of drug tolerability.

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An important aspect of tolerability is the vehicle because it can improve drug delivery, reducing drug concentration and thus decreasing irritation.[19] The ideal vehicle should combine humectant and occlusive ingredients to attract water and decrease transepidermal water loss, both of which may decrease irritation and enhance skin barrier repair, especially in individuals with sensitive skin.[20] In this supplement, Tanghetti,[21] Del Rosso,[22] and Draelos[23] discuss several available BPO products in novel vehicles that moisturize and decrease irritation.

Selection pressures on propionibacteria exerted by the use of antibiotics have led to a reexamination of the roles of other topical ingredients in the management of acne. Benzoyl peroxide in new vehicles, which have been designed to overcome some of the drawbacks of the earliest formulations, is undergoing a reexamination by the dermatologic community. It is our hope that this supplement will be useful to dermatologists who treat acne on a daily basis.

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The Evolution of Benzoyl Peroxide Therapy

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Since its first use in dermatology last century, benzoyl peroxide (BPO) has undergone a number of reformulations, each enhancing its efficacy, tolerability, or both. Benzoyl peroxide can be used as monotherapy or in combination with oral or topical antibiotics or topical retinoids. Its antimicrobial activity is based on the generation of highly reactive oxygen radicals, a physicochemical effect to which Propionibacterium acnes *has not developed resistance. In addition to its nonspecific antimicrobial activity, BPO has keratolytic, comedolytic, and anti-inflammatory activity in acne. Benzoyl peroxide can be added to antibiotic regimens to help maintain bacterial sensitivity to the antibiotic. Additive or synergistic effects of BPO-antibiotic combinations have been demonstrated. Fixed combinations of BPO with either antibiotics or a retinoid recently have become available and may improve compliance. New moisturizing vehicles and stabilized BPO formulations also have added to tolerability and convenience. Benzoyl peroxide may have underappreciated potential to treat noninflammatory acne as monotherapy or in combination with a topical retinoid, an important antibiotic-sparing strategy.*

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Since its first use in dermatology last century for wound healing and antisepsis, benzoyl peroxide (BPO) has undergone a number of reformulations, each enhancing its efficacy, tolerability, or both. It is now the most widely used topical acne treatment.[1] There are more than 100 BPO products available in the United States in both over-the-counter and prescription formulations ranging in concentration from 2.5% to 10%. Vehicles include leave-on micronized gels, liquids, creams, washes, and solvent-based systems, and diverse delivery systems include tubes, pumps, jars, pads, soaps, and masks.

The most recent generation of BPO products includes fixed combinations with either an antibiotic or retinoid and reflects the current understanding of the role of BPO in helping to control bacterial resistance to antibiotics as well as treating both inflammatory and comedonal acne. Current guidelines recommend not using antibiotic monotherapy but rather adding BPO to the regimen and also between courses of antibiotics.[2,3] Benzoyl peroxide is a nonspecific antimicrobial agent acting through the generation of oxygen radicals that alter the microenvironment of the follicle and disrupt cellular function.[1,4] *Propionibacterium acnes* has not developed resistance to BPO, most likely because of the oxidation process of this agent.[5] Thus BPO is useful in antibiotic regimens for reducing resistant bacterial populations so that most bacteria remaining are antibiotic sensitive.[6]

Several studies have shown that the combination of BPO and topical erythromycin or clindamycin is synergistic and more efficacious than either agent alone.[7-9] Combination therapy also may improve tolerability.[10] Lastly, the convenience of a once-daily BPO and antibiotic fixed combination simplifies the regimen and therefore can be expected to enhance compliance and efficacy.[11]

BPO Activity in Acne

Benzoyl peroxide has antibacterial, keratolytic, comedolytic, and anti-inflammatory activity in acne.[12,13]

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Cove and Holland[1] found that BPO was lethal to 9 cutaneous commensal bacteria; *P acnes* was most sensitive to BPO. Benzoyl peroxide is a powerful oxidizing agent,[14] and it has been suggested that oxidation by BPO causes the release of reactive oxidized intermediates that alter the microenvironment of the follicle and disrupt cellular function, thus killing them.[1,4] The antibacterial effects of BPO have been attributed to its ability to inhibit metabolic function, alter protein synthesis, induce ornithine decarboxylase activity, cause DNA strand breakage and suppress its synthesis, and interfere with mitochondrial respiration.[4]

In an in vitro study of the bacteriostatic activity of BPO, Fanta and colleagues[15] measured the areas of inhibition produced in agar plates by BPO 5% and BPO 10% in an alcohol-based gel and ethanol suspensions versus vehicle and alcohol-free vehicle as well as aqueous solutions of erythromycin and tetracycline at different concentrations. After 5 days, both concentrations of BPO produced similar areas of inhibition; the areas also were similar to both vehicles. Dramatically smaller areas of inhibition were produced with the alcohol-based suspensions of BPO. The vehicle greatly contributed to the bacteriostatic effect of BPO.[15]

Benzoyl peroxide also has keratolytic activity, which contributes to its efficacy in comedonal acne. Keratolytic activity in acne treatment does not actually lyse keratin but rather helps reduce the cohesiveness of the cells of the stratum corneum (SC), thus improving topical drug delivery through the epidermal barrier. Waller and colleagues[13] compared the keratolytic activity and degree of barrier disruption of BPO 2% and retinoic acid (RA) 0.05% to salicylic acid (SA) 2% (a well-established keratolytic). In addition, untreated skin, as well as unoccluded, occlusion, and vehicle controls, were evaluated. Sites on the volar aspect of the forearms were tested in 6 white volunteers (mean age, 55.2 years) and examined at 3 and 6 hours postapplication. At each site, 25 tape strips were removed and the amount of SC removed was assessed.[13]

At 3 hours, BPO 2% removed 21% more SC than RA 0.05%.[13] At 6 hours, the treatments were similarly effective. This study also revealed that the onset of keratolytic activity was apparent within a few hours of BPO application and more rapid than SA and RA. The tape strips were removed in groups of 5, and it also was shown that SA was most effective for superficial keratolysis, suggesting that it may be most effective for mild acne, while BPO was more effective at superficial and deeper levels of the SC and may have its greatest efficacy against deeper, more pustular lesions. The authors also noted that the greater ability of BPO to penetrate the SC may improve the penetration of coadministered drugs, which also serves to explain the increased efficacy seen with BPO-antibiotic treatment as well as topical retinoids. Because of its greater barrier disruption, BPO was more likely to be drying.[13]

BPO Fixed Combinations With Antibiotics

Currently, antibiotic and BPO fixed combinations include erythromycin 3%–BPO 5% (E/BPO) and clindamycin 1%–BPO 5% (C/BPO). The first combination was an E/BPO gel that is premixed by the pharmacist prior to dispensing and must be refrigerated by the patient and discarded after 3 months. It has been suggested that topical erythromycin is more likely to encourage the development of bacterial resistance than clindamycin.[16] The next generation was a twice daily water-based C/BPO formulation that also is compounded by the pharmacist but can be kept unrefrigerated for 3 months; another improvement followed—a factory-mixed once-daily gel that can be stored by the patient at room temperature for 2 months. The factory-mixed product can be refrigerated to expand its use to up to 2 years. This vehicle is moisturizing through the addition of glycerin as a humectant to draw water from deeper layers to the skin surface, and dimethicone as an occlusive to prevent further transepidermal water loss due to barrier disruption from the BPO.

Efficacy and Tolerability of BPO-Antibiotic Fixed Combinations

An improvement to the original E/BPO formulation was a single-dose packaging system consisting of 2 pouches, one containing BPO 10% and the other containing erythromycin 3%. When the contents of both pouches are mixed in the palm of the patient's hand, a single dose of E/BPO is formed. A multicenter randomized trial of this product versus vehicle was conducted in 223 participants with moderate to severe acne for 8 weeks.[17] At 8 weeks, there were −69.2% and −48.1% reductions in inflammatory lesion counts in the E/BPO (n=112) and vehicle (n=111) groups, respectively. However, reductions in comedonal lesion counts were similar between treatment groups, with a trend toward greater comedonal lesion count reduction with E/BPO. At 8 weeks, treatment success, defined as clear or sparse comedones with no or few inflammatory lesions, was achieved in

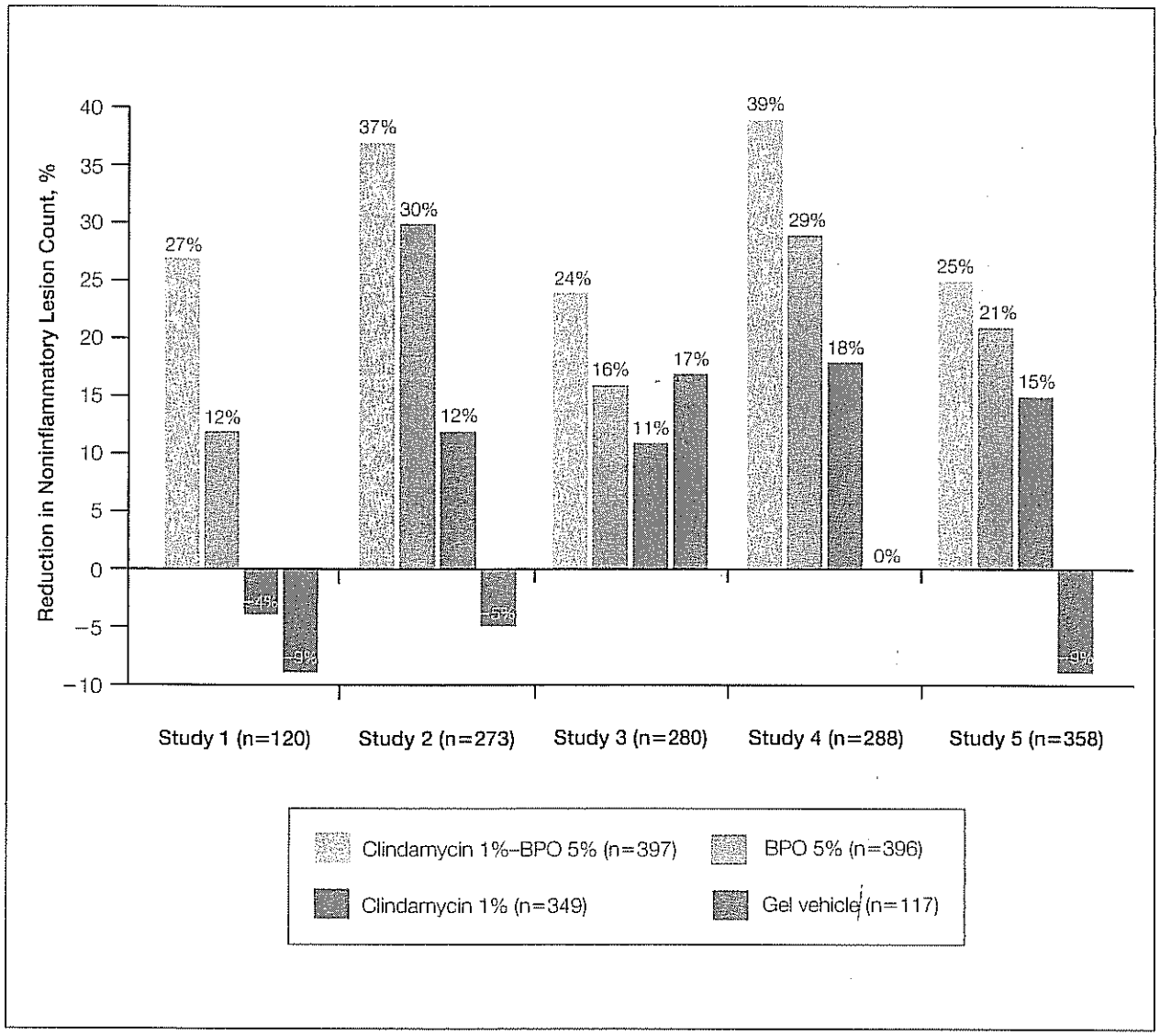

Figure 1. Mean percentage reduction in noninflammatory lesion counts. BPO indicates benzoyl peroxide. Adapted with permission from Stiefel Laboratories, Inc.[18]

34.8% of participants in the E/BPO treatment group and 14.4% of the vehicle group ($P \leq .001$).[17]

The efficacy of C/BPO gel has been demonstrated in several studies. In a 16-week, single-center, double-blind, randomized, parallel-group study, twice daily C/BPO was compared with twice daily clindamycin gel 1% monotherapy in 79 participants.[8] By week 16, the combination gel was superior to clindamycin monotherapy in total lesion count reduction ($P=.013$). As early as week 8, the median percentage reductions from baseline in both inflammatory lesion and comedone counts were significantly greater with the combination gel versus clindamycin monotherapy ($P=.014$ and $P=.018$, respectively). At week 8, the total lesion count reduction was −40.7% for the combination gel and −14.0% for clindamycin monotherapy ($P=.006$), and by study end at week 16, the percentage reductions were −52.7% and −27.5%, respectively ($P=.013$).[8]

In another double-blind randomized trial enrolling 334 participants, once daily C/BPO (n=95) was compared with each of its components (BPO, n=92; clindamycin n=89) and vehicle (n=58).[9]

At week 11, 66% of participants treated with C/BPO had a good or excellent global response versus 41% of the BPO monotherapy group, 36% of the clindamycin monotherapy group, and 10% of vehicle-treated controls. Clindamycin-BPO was found to be superior to the other treatments for reduction in inflammatory lesion counts and global improvement scores. It also was superior to BPO monotherapy in percentage reduction in noninflammatory lesion counts, and both C/BPO and BPO were superior to clindamycin and vehicle in reducing noninflammatory lesion counts.[9]

The results of this study suggest that most of the comedolytic effect seen with treatment was due to the effect of BPO.[9] All treatments were well-tolerated, with no statistically significant differences between the local irritant effects of the active treatments versus the vehicle. Peeling was significantly worse in participants receiving C/BPO compared with clindamycin monotherapy ($P<.02$), but erythema was worse in the BPO monotherapy group. The fact that erythema was less in the combination group may be attributed to the anti-inflammatory effect of clindamycin. The combination C/BPO gel in this study was formulated in a premixed stable gel that did not require refrigeration and contained glycerin and dimethicone. This combination vehicle was designed to produce synergistic moisturization whereby glycerin attracts water from the viable skin layers and dimethicone prevents evaporation of cutaneous moisture. The vehicle also can obviate the use of other moisturizers.[9]

Figure 1 shows the mean percentage reduction in noninflammatory lesion counts at week 11 from 5 studies conducted during phase 3 trials comparing once daily C/BPO with each of its components and vehicle.[18]

A study comparing C/BPO gel, clindamycin phosphate solution 1%, and vehicle gel found that the combination also has excellent antipropionibacterial efficacy.[19] The study population consisted of 60 healthy volunteers with high facial *P acnes* levels but without clinical acne. Treatment with C/BPO produced 91% inhibition of *P acnes* levels 24 hours after application. By the end of the 2-week study, C/BPO had produced a 99.9% inhibition from baseline in *P acnes*. In comparison, a significant reduction in bacterial load was not observed with clindamycin monotherapy until the end of the study at week 2, with 77% inhibition noted ($P<.05$). Participants using vehicle gel had no apparent reductions in bacterial load.[19] This study underscores the increased rapidity of results that can be obtained when BPO is added to topical clindamycin.

The tolerability of the once daily C/BPO gel with moisturizing excipients was compared to the twice daily C/BPO gel formulation without added moisturizing ingredients.[10] A total of 62 participants were enrolled in the 2 studies. After 1 week of treatment, both products appeared to be well-tolerated with little erythema, peeling, or dryness. However, C/BPO with moisturizers caused significantly less peeling ($P=.045$) and dryness ($P=.059$), and substantially less erythema. There also was significantly less burning reported by participants at week 1 with the moisturizing C/BPO formulation ($P=.034$).[10]

BPO Combination Therapy for Mild to Moderate Acne

It appears that the comedolytic activity of BPO may have been overlooked. Specifically, the 2003 acne consensus guidelines recommend topical retinoids as first-line therapy for comedonal acne, with either azelaic acid or salicylic acid as alternatives.[2] Yet several studies of BPO alone as well as in combination with and in comparison to a retinoid indicate that this agent has substantial anticomedolytic properties.[9,17,18] It is possible that the increasing issue of bacterial resistance will force a reappraisal. In a review of the significance of resistance in acne treatment, Eady and colleagues[6] stated:

> [E]xpert opinion is beginning to shift away from antibiotics towards a greater reliance on topical alternatives, especially for acne that is mild or localized. . . . The best way forward is to accept that some reduction in antibiotic usage is advisable and that, as in other areas of medicine, antibiotics should not be given unnecessarily. This means considering alternatives for which the risk-benefit profile is at least as good as that of antibiotics.

While the acne consensus guidelines list topical retinoids as first-line therapy for mild to moderate acne (along with oral contraceptives for appropriate patients), the algorithm proposed by this group emphasizes that BPO should be added. Nonantibiotic treatments, such as BPO and/or a retinoid, are preferred to antibiotics for

mild acne with small, superficial, and localized inflammatory lesions and comedones. For moderate acne with numerous or widespread inflammatory lesions, some being large or deep, a single course of oral or topical antibiotic therapy is recommended in combination with BPO and a topical retinoid.[6]

BPO-Retinoid Combination Therapy

The use of BPO-retinoid combination therapy as an antibiotic-sparing strategy is rational and may be especially useful in mild to moderate acne without a strong inflammatory component. Topical retinoids, like BPO, are effective comedolytics and some, principally adapalene, also may have anti-inflammatory activity.[12] Also, as recommended by the 2003 Global Alliance to Improve Outcomes in Acne, it is rational to use multiple agents with different but complementary modes of activity to address several acne pathogenetic mechanisms.[2] Accordingly, a new fixed-dose once-daily gel combining adapalene (AP) 0.1% and BPO 2.5% has been formulated and is awaiting US Food and Drug Administration approval. Clinical trials showed this fixed combination had a clinical profile similar to its 2 components.[20] In a recent study, 60 participants were randomized to treatment with the AP 0.1%–BPO 2.5% fixed-combination product and either BPO 2.5% or BPO 5%, or AP 0.1%–BPO 5% versus BPO 5% or BPO 10%.[21] The overall cutaneous tolerability profile was best with the AP 0.1%–BPO 2.5% fixed-combination product, which was similar to BPO 2.5% or

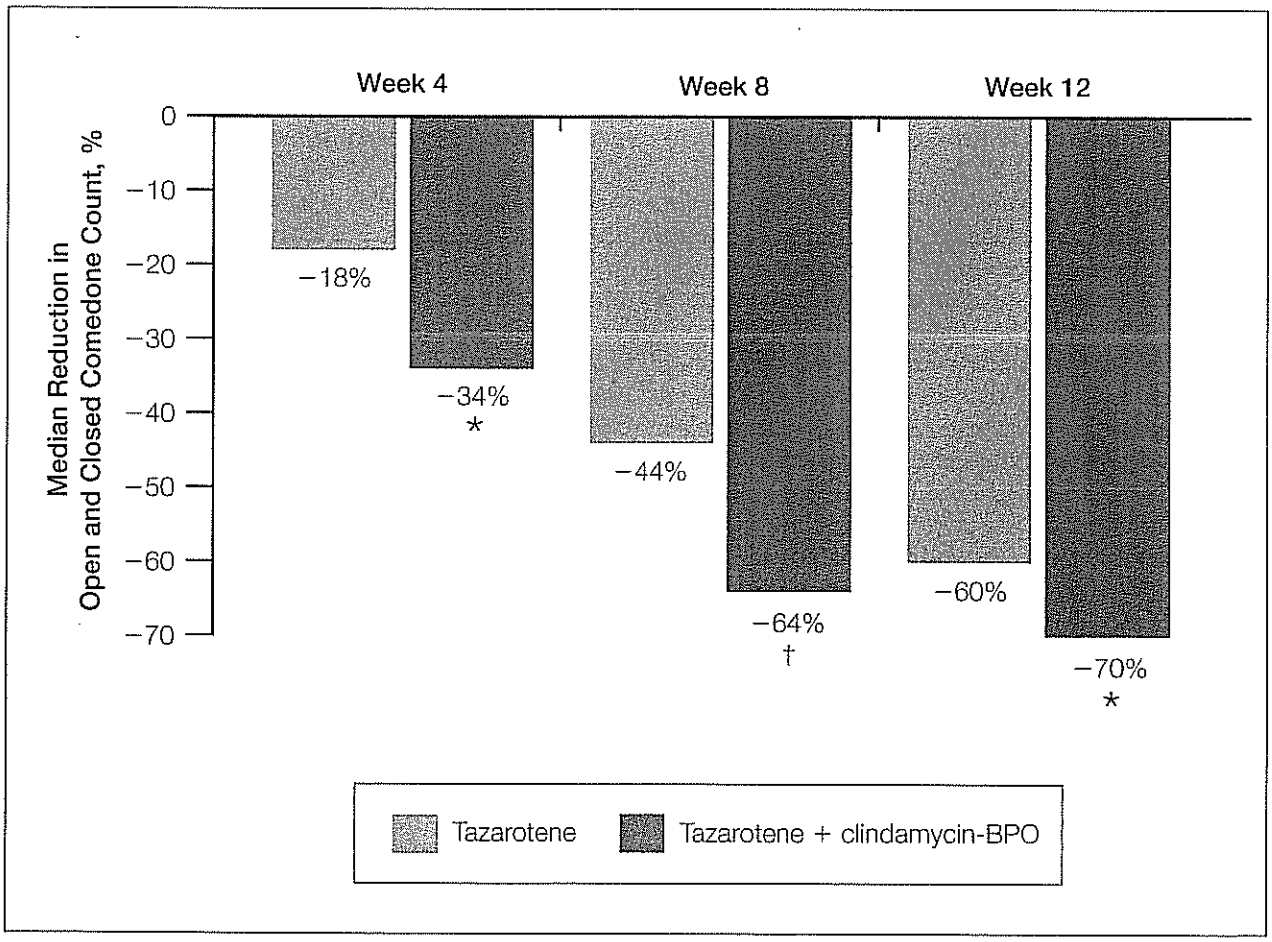

Figure 2. Reduction in total comedonal lesion counts (open and closed comedones) with tazarotene cream 0.1% in combination with clindamycin 1%–benzoyl peroxide (BPO) 5% gel versus tazarotene cream 0.1% monotherapy. Asterisk indicates $P \leq .01$; dagger, $P \leq .001$ vs tazarotene alone. Reprinted with permission from *The Journal of Drugs in Dermatology.* Copyright 2006.[24]

BPO 5% monotherapy. Although not proven in clinical practice, this study found that the AP 0.1%–BPO 2.5% fixed-combination product was optimum because it contained the lowest effective dose of each component.[21]

Pariser and colleagues[22] evaluated the long-term safety and efficacy of the AP 0.1%–BPO 2.5% fixed-combination product in 452 participants for up to 12 months. In the intention-to-treat population, the median percentage reduction was 70% for noninflammatory lesions, 76% for inflammatory lesions, and 70.8% for total lesions. Dermatologic adverse events were mild to moderate overall, with most occurring during the first 3 months of the study (23% of total of 29%).[22]

In another study, the efficacy and tolerability of BPO gel 4% used twice daily and AP gel 0.1% used once daily were compared in 178 participants with acne.[23] Benzoyl peroxide produced a significantly more rapid reduction in noninflammatory lesion counts at weeks 2 and 5 versus AP alone ($P<.0001$ and $P=.0049$, respectively) and was still superior at week 8. By week 11, the reduction in noninflammatory lesion counts was slightly better in the AP 0.1% group. Benzoyl peroxide also was significantly superior to AP in the reduction of inflammatory lesion counts at weeks 2 and 5 ($P=.0033$ and $P=.0187$, respectively). This rapid response, attributable to the BPO component, is important to note because rapidity of visible improvement remains important to patients with acne and their caregivers regardless of demographic. In this study, the largest number of study dropouts was in the AP treatment group, which the authors suggested may have been due to the longer latency to response, while the BPO component may compensate well for this onset.[23]

The C/BPO fixed-combination gel with 2 moisturizers used with tazarotene cream 0.1% was compared with tazarotene cream 0.1% and the moisturizing vehicle gel in 121 participants for 11 weeks.[24] Treatment with the combination therapy produced a significantly superior reduction in open and closed comedones beginning at week 4. The median reduction in total comedonal lesion counts at week 4 was −34% in the combination treatment group and −18% in the tazarotene monotherapy treatment group ($P\leq.01$). At week 12, the percentage reductions were −70% and −60%, respectively ($P\leq.01$)(Figure 2). Combination therapy also gave better results against inflammatory lesions, with median reductions of −30% and −22%, respectively, at week 4, and −63% and −58%, respectively, at week 12. Both regimens were well-tolerated with no significant between-group differences for peeling, burning, redness, dryness, facial discomfort, itching, or irritation. There was a slightly lower incidence of peeling and dryness with the combination treatment, which likely was due to the presence of the emollients in the C/BPO gel.[24]

Comment

Benzoyl peroxide, the most widely used acne treatment, is deserving of a new look by dermatologists. Its ability to help prevent the development of bacterial resistance to antibiotics used to treat acne is well-known, as are the recommendations to combine it with oral and topical antibiotics during acne treatment. The fixed combinations of BPO plus either topical erythromycin or clindamycin have shown that the combination is at least additive and possibly synergistic in its effects. Although the use of BPO to treat inflammatory acne lesions has long been promoted, it has excellent activity against open and closed comedones, which has received less attention. In the future, because of the resistance issue, antibiotic-sparing strategies will be increasingly important, which is likely to give a more prominent place to BPO, alone or in combination with a variety of known therapeutic regimens, and also may suggest a review of the fixed combinations available now and in the future. Additionally, the new BPO vehicles have been developed to reduce irritation and improve the convenience of use.

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