A Current Review of Topical Benzoyl Peroxide: New Perspectives on Formulation and Utilization

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KEYWORDS

- Benzoyl peroxide • Topical use • Acne
- Combination therapy • Antibacterial resistance

Sales of over-the-counter benzoyl peroxide (BPO) are currently approaching $1 billion annually, effectively securing its position as the most widely used topical acne medication in dermatology. Its safety and efficacy are unquestionable. Because it has been many years since this product was thoroughly reviewed in the literature, this article provides the most recent perspectives regarding the topical use of BPO in dermatology.

BPO is an organic peroxide consisting of white crystal agglomerates that are soluble in chloroform and other organic solvents but insoluble in water.[1] Although stable at room temperature, it is flammable[2] and is explosive when heated to temperatures of greater than 100°C.[3]

Although a powerful oxidizing agent, it is nontoxic to humans and is used in food processing to bleach flour and oils and in various industrial applications.[1] BPO, derived from a byproduct of coal tar, was used as early as 1905 as a nonirritating oxidizing antiseptic. Although BPO was mainly used as a bleach for flour in the first part of the 20th century, dermatologists also prescribed it for wound healing and treating burns and chronic skin ulcers.[4]

PHARMACOKINETIC AND SAFETY PROFILE

A study by Nacht and colleagues[5] examined BPO penetration through normal skin and its systemic disposition. A study of radiolabelled BPO penetration through excised human skin found that under maximal steady state conditions, 4.5% of the applied dose was delivered to the skin in an 8-hour period. Of the total amount of BPO applied topically, 95.5% was recovered unchanged from the skin at 8 hours. Topically applied BPO was found to penetrate unchanged through the stratum corneum or into the follicles. It then diffused into the epidermis and dermis, where it is converted to benzoic acid, possibly with the aid of follicular bacteria. Systemically, studies in primates showed that benzoic acid is absorbed as benzoate and excreted unchanged in the urine. BPO seems to avoid degradation by the liver.[5]

Haustein[6] studied 100 patients aged 12–28 years who had acne treated with 10% BPO gel twice daily for 8 weeks. Before treatment, they were tested with BPO 5%, 1%, and 0.1% embedded in paraffin for 24 hours, and results were read at 24, 48, and 72 hours. Of the 100 patients, only

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Dermatol Clin 27 (2009) 17–24
doi:10.1016/j.det.2008.07.001

2 reacted to the BPO 1%, whereas the 0.1% test concentration gave only a questionable reaction. These results suggest that BPO is a weak allergen and is more likely to give an irritant reaction, especially at higher concentrations.

Six patients (6%) complained of stinging, itching, burning and erythema, edema, dryness, and desquamation at treatment initiation. These symptoms disappeared in 5 patients with continued use, including after a short break. In addition to these study findings, clinical experience suggests that BPO, at the concentrations usually used in practice, is most often associated with irritant reactions that often resolve with a drug holiday. True contact dermatitis can occur but is relatively uncommon. These studies highlight the importance of the delivery systems and vehicles used in clinical practice.

ANTIBACTERIAL AND ANTI-INFLAMMATORY PROPERTIES OF BENZOYL PEROXIDE IN ACNE

BPO has been shown to have numerous modes of activity. This remarkable drug has been shown to possess antimicrobial and anti-inflammatory,[7] keratolytic,[8] and wound-healing activity.[9,10] How BPO affects sebum secretion rate remains controversial.[11–14] However, current thinking maintains that no topical agents are sebostatic.[15,16]

Antimicrobial Activity

Over the years BPO activity in acne has been shown to be caused by antimicrobial activity that is rapid and bacteriostatic and possibly bactericidal.[15] In 1974, Fulton and colleagues[17] compared the antibacterial activity of BPO and vitamin A acid. They noted that BPO "is more than just another epidermal irritant; it is also a potent bacteriostat."[17] They also noted that the vehicle is critical. In the alcohol gels studied, residual deposition of BPO on the skin after the alcohol vehicle evaporated allowed continued contact.

In vivo studies comparing *Corynebacterium acnes* recovery from sebum in 10 subjects applying BPO 10% in alcohol gel vehicle twice daily and vehicle twice daily found a marked reduction in bacteria in the sebum of those using active treatment (Bollinger JN, Rowlands JR, Gause EM, personal communication). This group found that BPO also decreased the ratio of free fatty acids to free esters in sebum. Currently, the role of free fatty acids in acne pathogenesis is no longer considered important.[1]

A study by Cove and Holland[18] in 1981, examined survival curves of 8 different microorganisms known to colonize skin in the presence of BPO. The microorganisms varied in increasing sensitivity to BPO as follows: *Propionibacterium acnes, Staphylococcus capitis, S epidermis, S hominis, P avidum, P granulosum,* and the yeast *Pityrosporum ovale*. BPO had a homogenous bactericidal effect, suggesting that no resistant subpopulations were present. The authors point out that BPO exerts its bactericidal activity through oxidation, leading to the release of highly reactive oxygen intermediates that oxidize proteins in bacterial cell membranes.[18]

A study using high-pressure liquid chromatography 1 to 2 minutes after application of BPO emulsion to the skin found that BPO rapidly penetrates the stratum corneum. Additionally, BPO is degraded to benzoic acid, leaving no detectable BPO depot in the stratum corneum.[19]

Burkhart and Burkhart[20] showed that *P acnes* are capable of secreting protective biofilm polysaccharides, which may explain some of the difficulty of delivering effective levels of antimicrobials within the skin. BPO, with its oxidative properties, appears to have a role in destroying this biofilm. This biofilm model helps to illustrate the use of BPO in facilitating the delivery of topical antibiotics and other agents to the targeted bacteria.[20,21]

Although this biofilm model is intriguing, the clusters of *P acne* and other bacteria are encased in a matrix of sebum and keratin, which acts as a barrier to the delivery of therapeutic products as well as provides for an anaerobic environment. Here again, the oxidative and keratalytic properties of BPO provide utility in weakening this protective barrier. Perhaps the final word and summary of the current data on the antibacterial efficacy of BPO in acne should go to Kligman,[22] who declared in 1995 that "No prescription antibiotic can begin to match the antibacterial efficacy of benzoyl peroxide. Twice-daily applications for five days will reduce the *P acnes* population by more than 95%! Moreover, unlike the case with topical antibiotics, *P acnes* has not been smart enough to evolve resistance to benzoyl peroxide."

Keratolytic Activity

An important and often overlooked property of BPO is its effect on comedonal acne. A study by Waller and colleagues[8] compared the keratolytic efficacy and cutaneous barrier disruption of BPO 2%, retinoic acid 0.05%, and salicylic acid 2%, a well-established keratolytic. Sites on untreated volar forearms of volunteers were treated under occlusion and unoccluded and examined at 3 and 6 hours. At 3 hours, BPO was significantly more keratolytic, as shown by the amount of stratum corneum removed with tape stripping.

Transepidermal water loss (TEWL) was used to study barrier disruption, which was found to correlate with the depth of stratum corneum removal. Salicylic acid had the greatest keratolytic activity at more superficial depths.

Perhaps because of the vehicle used in this study, BPO was more effective and created a higher TEWL effect at deeper layers. This effect was seen as a complement to its known antibacterial efficacy. The authors also note that the ability of BPO to disrupt the stratum corneum barrier may improve penetration of drugs that are coadministered.[8]

CLINICAL STUDY REVIEW

Benzoyl Peroxide Monotherapy

The first use of BPO in the management of acne was reported by Canadian dermatologist William Pace,[23] who identified it as the active ingredient in a chlorhydroxyquinolin ointment in a petrolatum base (Quinolor Compound Ointment, ER Squibb and Sons). After discussing BPO solubility issues with John King, Pace then consulted a London, Ontario pharmacist, Clare Munro, and incorporated the solution of BPO to a commercial cream base (Dermabase, Borden, Ltd., Don Mills, Ontario, Canada). This pharmacy-compounded product was reported by Pace to be as effective as the original but much less irritating, and formulated into an aesthetically acceptable, clinically efficacious acne treatment.

The effectiveness of Pace's cream came to the attention of Werner Stiefel who commercialized BPO for the treatment of acne. Stiefel, who was educated as a chemical engineer, engaged the team of Cox and Ciufo,[24] who created and patented a stable composition of BPO for the treatment of acne.

Since then, many BPO antiacne products have been marketed. Dosage forms include gels, cream, lotions, aerosols, foams, wipes, pads, masks, and solutions. Concentrations have varied from around 1% to as high as 20%. Various drug delivery systems have also been used with BPO, including micronization, polymeric drug release, encapsulation, entrapment, particle coating, cosolvent systems, combinations with other actives, combinations of actives to address different therapeutic needs, and copackaging with companion products.

From the regimen of sulfur with BPO and then onto combinations with salicylic acid, sunscreens, antibiotics, and barrier repair agents, dermatologists have recognized that treatment of skin conditions often requires combination therapy to address the multifaceted causes seen in skin disease. Inventors and companies have been searching for the utopian treatment for acne, but to no avail. Efforts have been directed toward addressing the technical deficiencies that are common with BPO products.

Skin irritation is the main issue observed by patients and physicians when BPO is used to treat acne. Irritation potential may be reduced through micronizing the BPO particle or making it softer and less abrasive. Other additives, such as emollients, polymers, and anti-irritants, may be included in the compositions to improve the product's aesthetics. Furthermore, the rate of release of the drug and physical availability of the active may also be modified through drug delivery approaches, such as encapsulation, coating technologies, and entrapment.

Although early BPO products such as BenzaGel, Panoxyl, Desquam, and Persagel served dermatology well, they were essentially replaced with newer delivery systems. A product based on dimethyl isosorbide as a solvent for BPO was developed by dermatologist Richard DeVillez.[25] Seeing the need for the active to penetrate better, DeVillez found that BPO dissolved in dimethyl isosorbide and that stability could be maintained in these compositions. Won and colleagues[26] found that BPO could be entrapped in a porous styrene–divinylbenzene polymer structure, which is now known as microsponge technology. Both delivery systems reduced irritation.

Flynn[27] recognized the need to remove excess skin oils found around acne lesions and found fumed silica served this purpose. This concept became a major part of the Oxy acne franchise.

Cox and Ciufo, Young, Fulton, and Klein and Fox each contributed to the knowledge used to produce stable BPO compositions today.[24,28–30] Cox[24] recognized that having BPO at least partially suspended improved stability. He coupled this with the inclusion of an organic emollient and the reduction of the particle size of the drug crystal. Young[28] pioneered a hydroalcoholic gel that used polyoxyethylene-based surfactants to reduce product drag during application. Fulton[29] showed that using a high concentration of a polar emollient, glycerin, also resulted in not only a stable composition but also one perceived to be nonirritating. Klein and Fox[30] further found that stability improved if a small amount of dioctyl sodium sulfosuccinate was added to the formulation.

A new BPO product in a novel solvent-based system has been formulated that apparently, similar to those containing dimethyl isosorbide, has the ability to solubilize BPO and facilitate a rapid and more complete absorption of the BPO. Results of two recent trials suggest a more rapid response in treating comedones with similar

efficacy in treating inflammatory lesions to a 5 percent water-based benzyl peroxide/clindamycin combination. This new solvent system did show a significant increase in stinging, burning, erythema, and dryness during the first two weeks. It is possible that the volatile agents in this product are also solubilizing the lipids in the comedones, resulting in an unusually rapid response for comedonal acne.

There are an incredible number of new and old benzyl peroxide products available today. There are many differences in these formulations, which could have a significant effect on delivery tolerability and efficacy. Well-designed head-to-head studies that evaluate these products in a prospective manner are lacking. Therefore, it is difficult for comparative assessments on safety or efficacy across these different formulations to be made.

A single-blind comparison of the safety and efficacy of twice-daily BPO 4% gel and once-daily adapalene 0.1% gel showed that both treatments were similarly effective in treating comedonal and inflammatory lesions after 11 weeks. However, BPO 4% was statistically superior to adapalene 0.1% in the percentage reduction of all lesions at weeks two and five ($P = .0007$ and $P = .0944$, respectively). This difference is important because patients who have acne typically comply better with therapy if they see a rapid response. The similar effects of both BPO and adapalene on comedones in this study highlights the importance of BPOs in the treatment of this form of acne. In fact, the consensus groups' opinion does not even mention this class of products in the initial treatment of comedonal acne. Hopefully, renewed attention on this subject will permit a better appreciation of this point. Experts suggested that in BPO–retinoid combination therapy, the rapid upfront response to BPO compensated for the retinoid's later onset of action both for inflammatory and comedonal acne.[31]

In a comparison of 6% BPO gel and 1% clindamycin phosphate lotion, the BPO gel produced more rapid and significantly greater reductions in *P acnes* counts ($P < .01$) and fluorescence.[32]

The current trend in the management of acne is to combine BPO with other medications that have a different mode of action.[15] However, BPO monotherapy is still used particularly in the form of washes designed to be rinsed off rather than remain on the skin where they may be irritating. These washes are increasingly available in different strengths and various cleansing bases for patients with sensitive or irritation-prone skin. Experts have suggested that exposing the skin to an acne treatment is more important than the duration of exposure or the medication concentration. However, data supporting this in large controlled clinical trials are lacking. The authors' believe that leave-on products with slow-release BPO designed for longer skin contact are potentially more effective in affecting a positive clinical outcome.

Burkhart[33] suggested that the rapid effect of BPO washes may be from the ability of the BPO radicals to react with bacterial membranes and intracellular organelles within milliseconds of application. This approach may be especially effective, because overzealous washing and scrubbing of acne lesions may actually worsen the disease and increase irritation.[33,34]

Occlusive moisturizers act as an emollient to provide rapid repair of the skin barrier.[35] Occlusives alone are effective, but inefficient and not cosmetically acceptable. A humectant alone may exacerbate transepidermal water loss.[35] Occlusive agents, such as dimethicone, are designed to help prevent water evaporation, and glycerin, which is a humectant, attracts water from the dermis to the epidermis. These formulations combining a humectant with an emollient assist with rehydration and restoration of the epidermal defensive. Another strategy for improving the tolerability of BPO is to formulate it in a 10% urea base, which might moisturize the skin because of its humectant property[36] and add to its antiacne efficacy because of its keratolytic activity.[37]

Combination Therapy

Benzoyl peroxide and topical antibiotics

The success of both BPO and topical antibiotics in acne treatment prompted many studies of their combination to increase efficacy through combining drugs with differing but complementary modes of activity. Moreover, well-designed combination therapy may take advantage of the possible synergy between the effects of the agents chosen.[38] However, as *P acnes* resistance to topical and oral antibiotics began to increase worldwide, strategies were sought to minimize this threat. Topical combination therapy is prescribed using separate products, with many combinations, such as BPO with clindamycin or erythromycin, used to increase efficacy and decrease risk for resistance.[39,40]

In 1985, Klein's patent for the first combination of BPO with an antibiotic, erythromycin, was issued and with it came the birth of a product compounded by the pharmacist and dispensed to the patient (Benzamycin Topical Gel, Dermik). This product was to be refrigerated by the patient and discarded after 90 days. The next-generation product (BenzaClin Topical Gel, Dermik) is a mixture of

BPO 5% with clindamycin phosphate 1% that is similarly compounded by the pharmacist and can remain at room temperature for 90 days, after which it should be discarded by the patient. Another factory-blended BPO 5%/clindamycin phosphate 1% gel (Duac Topical Gel, Stiefel Laboratories) is available in a composition that is refrigerated by the distribution channel and then kept at room temperature by the patient for 60 days, after which it should be discarded. All of these products have been shown to be widely accepted by physicians and patients.

The 2003 acne treatment consensus guidelines state that oral and topical antibiotics should not be used as monotherapy in acne because chronic use is associated with the emergence of resistant bacterial variants.[15] In a study by Cunliffe and coworkers,[41] resistant *P acnes* appeared as early as 8 weeks after initiation of therapy with topical clindamycin monotherapy and increased over the 16 weeks of the study. The recent Scientific Panel on Antibiotic Use in Dermatology convened to evaluate the use of antibiotics in dermatology.[42]

Prolonged topical or oral antibiotic therapy for acne vulgaris is best accompanied by the use of BPO to optimize efficacy and mitigate the emergence of less-sensitive *P acnes* strains. The presence of less-sensitive *P acnes* organisms may contribute to decreased efficacy of antibiotic treatment in some patients, especially if a high density of these strains is present. However, oral antibiotics, such as doxycycline, minocycline, and topical clindamycin, have continued to maintain efficacy in many patients, specifically when used in appropriate combination with other agents, such as BPO and topical retinoids.

The use of combination therapy with BPO to help minimize the development of resistance is important to note in clinical practice. In more than 35 years of use in acne management, bacterial resistance to BPO has not developed.[15]

Several studies have shown the combination of BPO and a topical antibiotic was more effective and better tolerated than monotherapy with either agent.[41,43–46] A BPO 5%/clindamycin 1% pharmacy-compounded water-based gel is available, as is a premixed BPO 5%/clindamycin 1% in a dimethicone- and glycerin-containing gel. These gels were proven to be safe and effective in the treatment of acne. On evaluation of the reduction of inflammatory lesions at 11 weeks, the dimethicone- and glycerin-containing BPO/clindamycin gel used once daily and the BPO/clindamycin water-based gel used twice daily yielded similar results.

Cunliffe and coworkers[41] compared clindamycin 1%/BPO 5% gel with clindamycin 1% gel monotherapy. Again, combination clindamycin/BPO therapy produced significantly greater reductions from baseline in inflammatory lesion, total lesion, and comedone counts compared with clindamycin monotherapy ($P \leq .046$), and greater improvements in patients' and physicians' clinical global improvement scores. This study was particularly notable in showing a greater than 1600% increase in *P acnes* counts from baseline to week 16 in the group undergoing clindamycin monotherapy. In contrast, the group undergoing combination therapy showed decreases in resistant bacteria, which correlated with reductions in inflammatory and total lesions ($r^2 = 0.31$ and 0.28; $P = .016$ and 0.027, respectively). Both the total *P acnes* count and the clindamycin-resistant *P acnes* counts were decreased with combination therapy but not with clindamycin monotherapy.

A 2007 randomized, assessor-blind study compared the safety and efficacy of once-daily applications of topical clindamycin 1%/BPO 5% and twice-daily applications of erythromycin + zinc acetate administered for 12 weeks in 148 patients with mild to moderate acne.[47] The BPO/clindamycin combination showed an earlier onset of action; at week 1, the proportion of patients with at least a 30% reduction in non-inflammatory lesions was 31.5% for the BPO/clindamycin group and 17.3% for erythromycin/zinc. This trend continued until study end, although reductions in total lesion count were similar at termination (69.8% and 64.5%, respectively). Both treatments were well tolerated.

BENZOYL PEROXIDE AND RETINOIDS

Combination therapy with BPO and antibacterials is effective in reducing bacterial proliferation and countering inflammation. Because effects in comedonal acne have not been well described or characterized in clinical trials, it is prudent to combine BPO with topical retinoids, an already important mainstay in acne treatment with strong anticomedogenic and comedolytic activity.[7,15]

Retinoids normalize the desquamation of the follicular epithelium and prevent the formation of new comedones, the precursor to all acne lesions.[7,48] Retinoids also enhance the penetration of other topical drugs into the follicle.[8] The introduction of less-irritating retinoids and more-emollient vehicles has made this therapy extremely tolerable. For example, in a study by Shalita and colleagues,[49] a 6% BPO wash used in combination with 0.1% tretinoin microsphere reduced skin tightness compared with tretinoin monotherapy.

In another study, patients with moderate to severe acne using tazarotene 0.1% cream each evening and were randomized to morning

applications of either vehicle gel or a clindamycin 1%/BPO 5% gel containing the emollient dimethicone and the humectant glycerin.[50] The retinoid plus clindamycin/BPO regimen showed a significantly greater reduction in comedonal lesions than tazarotene monotherapy beginning at week 4, and continued to be statistically significant throughout the 12-week study. Again this finding highlights the importance of benzyl peroxide in the treatment of comedonal acne. Surprisingly, clinical significance in inflammatory lesions was only seen in patients who had more than 25 lesions. The clindamycin 1%/BPO 5% gel was better tolerated and patients experienced a lower incidence of peeling and drying compared with those treated with tazarotene cream monotherapy. This finding was particularly noticeable and statistically significant at week 4 during retinization. Similar findings were also noted in a study using the same humectants- and emollient-containing BPO/clindamycin gel in combination with the retinoid adapalene.[51]

A fixed-dose, once-daily combination gel with adapalene 0.1% and BPO 2.5% was recently developed (EpiDuo, Galderma Laboratories).[52] A 12-month study enrolled 452 subjects to assess the efficacy and safety of the combination. Reductions in total, inflammatory, and comedonal lesions began as early as week one. At 12 months, when data from the last observation carried forward were examined, the median percent reductions from baseline were 65%, 70%, and 66% in total, inflammatory, and comedonal lesion counts, respectively. Treatment was well tolerated overall, with only a 2.0% dropout rate from adverse events. Studies have not compared the efficacy or tolerance of this product compared with currently used regimens of a BPO and clindamycin/retinoid combination.

SUMMARY

BPO is arguably the most widely used topical treatment for acne, with more than 35 years of safe and effective use. A resurgence in the use of this agent has recently occurred, despite the development of effective antibiotic and retinoid regimens. This resurgence seems to from the increasing appreciation of the bactericidal and anti-inflammatory capabilities and anticomedolitic properties of BPO. Most importantly, however, unlike other antibacterial products, bacterial resistance to BPO has not yet been observed and is unlikely to happen. It is generally agreed that adding BPO is a sine qua non of antibiotic treatment of acne because of its ability to reduce the risk for resistance and its activity against both sensitive and resistant strains of *P acnes*.

Although earlier formulations of BPO were somewhat limited by irritation, new vehicles have greatly improved the tolerability of BPO monotherapy and combinations. Adding excipients such as urea and glycerin, and the emollient dimethicone to the base also improve tolerability. Intriguing new research suggests that combining BPO and antibiotics or other drugs containing tertiary amines may enhance the free radical formation believed to be the basis of BPO's bactericidal activity. Strategies such as this to boost the activity of BPO may eventually result in greatly reduced antibiotic use in managing acne.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the editorial assistance of Stacey Moore at Physician Resources, LLC.

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