THE CLINICAL IMPACT OF VEHICLE TECHNOLOGY USING A PATENTED FORMULATION OF BENZOYL PEROXIDE 5%/CLINDAMYCIN 1% GEL: COMPARATIVE ASSESSMENTS OF SKIN TOLERABILITY AND EVALUATION OF COMBINATION USE WITH A TOPICAL RETINOID

James Q. Del Rosso DO FAOCD,[a] Emil Tanghetti, MD[b]

a. Clinical Assistant Professor, Department of Dermatology, University of Nevada School of Medicine, Las Vegas, NV

b. Clinical Professor, Department of Dermatology, University of California at Davis, Davis, CA

Abstract

A major challenge encountered in clinical practice in patients with acne vulgaris is irritation related to topical medications used for treatment. Advances in vehicle technology have improved formulations containing active ingredients known to produce irritation in some patients, such as benzoyl peroxide (BP) and topical retinoids. Clinical studies, including combination therapy studies have demonstrated that certain additives, such as silicates and specific humectants, reduce irritation by maintaining barrier integrity. A patented gel formulation of BP 5%/clindamycin phosphate 1% (clindamycin) containing dimethicone and glycerin has been studied both as a monotherapy and in combination with topical retinoid use. This article evaluates specific vehicle additives included in this gel formulation and explains their role in reducing irritation. Data from clinical trials utilizing this technology in acne management are also reviewed.

Introduction

Advances in formulation technology have resulted in the development and release into the marketplace of multiple active ingredients formulated in aqueous-based gels that are clinically effective and applicable to essentially all skin types.[1] These newer gel vehicles do not carry the "stigma" of predictable irritation, dryness and/or peeling that has characteristically been associated with the term "gel," as evidenced by results reported in controlled studies and experience from clinical practice. Examples of newer aqueous-based gel formulations associated with favorable skin tolerability profiles include adapalene 0.1%, metronidazole 0.75% and BP 5%/clindamycin 1% (tube gel formulation). Details related to the last formulation are discussed below.

Epidermal Barrier Considerations

Healthy appearance of the skin, maintenance of water content and balance, and continued barrier integrity allow for continuation of ongoing physiologic and enzymatic functions that support the epidermis as a dynamic unit.[2-7] Endogenous factors (ie, underlying disease states, physiologic aging) and exogenous insults to skin (ie, adverse climate, topical irritants, specific topical formulations, or medications) that impair barrier integrity and function require a series of repairs in order to return the epidermal barrier to its normally functioning physiologic state.[3-7] Physiologic repair mechanisms exist to replenish the intercellular lipid layer and are initiated by a sensitive homeostatic signal that recognizes increased transepidermal water loss.[3-6]

The epidermal barrier is composed of a cellular lattice of keratinocytes ("bricks") and an intercellular lipid bilayer matrix ("mortar") that surrounds the keratinocytes.[5-9] Within the keratinocytes, a hygroscopic collection of substances, collectively referred to as "natural moisturizing factor" (NMF), help to retain epidermal water content.[3-5,9] Also within the keratinocytes of the upper epidermis, specialized structures (lamellar bodies) form the intercellular lipid bilayer that functions as a permeability barrier regulating transepidermal water loss; epidermal enzymes, dependent on adequate water content, degrade attachments between corneocytes (corneodesmosomes), allowing for physiologic desquamation.[5,9-14] In the presence of epidermal barrier disruption, inclusion of well-formulated moisturizing components in topical vehicles can act in a manner similar to endogenous epidermal lipids in promoting and restoring epidermal barrier function, thus assisting the physiologic mechanisms that are upregulated to repair barrier integrity.[5,7,8,11-13] Proper combination of vehicle ingredients, including compounds with humectant, emollient, and occlusive properties, is a vital component of optimal vehicle design.[2-5,6-8]

The keratinocyte lattice and intercellular matrix components of the epidermal barrier work in harmony to:

(1) Maintain epidermal water transfer, balance, and physiologic content (20%-35%).

(2) Synthesize lipids in proper ratio and composition to create the intercellular bilayer. As cornification occurs in the upper epidermis, the intercellular lipid layer is converted to a ceramide-rich bi-layered membrane.

(3) Promote orderly progression of keratinocytes as they transcend the epidermis from the basal layer to the skin surface ending in physiologic separation and shedding of superficial corneocytes.

Significance of Vehicle Components in Topical Acne Therapy

It is well recognized that several medications used in topical acne treatment, such as topical retinoids, BP, alpha-hydroxy acids, and salicylic acid, may create cutaneous irritation related at least partially to epidermal barrier insult.[5,15,16] This is expressed visibly as dryness, redness, peeling and/or flaking with patients often expressing symptoms of stinging, burning, or skin being "more sensitive."[5,15] The use of gentle skin cleansers and moisturizers has been shown to significantly reduce signs and symptoms of skin irritation in patients treated with topical therapies for both acne vulgaris and rosacea.[15,16] As a result, the inclusion of vehicle components in topical treatments for acne vulgaris and rosacea, which are designed to reduce barrier impairment and optimize skin moisturization, is a logical and important approach in product design.

The BP 5%/clindamycin 1% tube gel formulation includes both glycerin, a humectant, and dimethicone, an emollient with occlusive properties. Inclusion of these components, which are commonly used in moisturizers and skin protectants, appears to limit irritation potential associated with topical acne treatment with data supporting this concept reviewed below. Glycerin is a humectant commonly used in moisturizer formulations, exhibiting favorable properties that promote maintenance of skin hydration and barrier integrity.[17,18] It is important to recognize that a humectant agent should always be combined with components that impart occlusive properties because skin application of a humectant alone without accompanying occlusivity may result in an increase in transepidermal water loss.[3-6] Emollients with occlusive properties, such as dimethicone, also serve to improve the cosmetic characteristics of the vehicle.[6] The enhanced elegance and reduced greasiness they provide for the overall product as compared to pure occlusive agents such as petrolatum may be appreciated after topical application and often relate directly to consumer product preference.[3-6] Interestingly, dimethicone has also been shown to significantly reduce symptoms of cutaneous irritation associated with chemical sunscreens.[19]

Clinical Studies

Topical BP 5%/clindamycin 1%, approved by the Food and Drug Administration (FDA) for treatment of acne vulgaris, is available in 2 aqueous-based gel formulations. One formulation requires compounding before dispensing in a jar (jar gel) and is approved for twice daily use. The other formulation, which does not require compounding before dispensing, is available in a tube (tube gel), and is approved for once daily use. The clinical efficacy of both formulations is well established. Marked nominal and percent reduction of inflammatory acne lesions were observed with the BP 5%/clindamycin 1% tube gel formulation applied once daily over an 11-week period as compared to reductions observed with either BP 5% or clindamycin 1% used as monotherapy in double-blind, vehicle-controlled, randomized, parallel studies; reduction in noninflammatory lesions was also observed with the highest trend noted with the combination product (Table 1).[20]

Skin Tolerability/Patient Preference Data

Two independently performed investigator-blinded, split-face, randomized studies of 61 patients, compared the cutaneous tolerability of both the tube gel and jar gel formulations of BP 5%/clindamycin 1%, applied over a 1-week period once daily and twice daily, respectively.[21] Overall, both formulations were well-tolerated; however, statistically significant differences were noted between the formulations for several skin tolerability parameters. The tube gel formulation was associated with statistically less peeling (P=.045), burning (P=.034), and dryness (P=.059) than the jar gel. Preference

Table 1. Combined Study Results.[20] Mean % Lesion Count Reduction and Mean Global Improvement Scores. BP 5%/Clindamycin Phosphate 1% Tube Gel vs. Clindamycin Phosphate 1% Gel vs. BP 5% Gel vs. Vehicle Gel: Application Once Daily x 11 Weeks.

Drug/Patient Number	Reduction Inflammatory Lesions	Reduction Noninflammatory Lesion	Global Improvement Score*
Benzoyl Peroxide/Clindamycin (Tube Gel) N=95	61 ± 3%	36 ± 4%	66%
Benzoyl Peroxide Gel N=92	39 ± 4%	30 ± 4%	41%
Clindamycin Gel N=89	35 ± 5%	9 ± 6%	36%
Vehicle Gel N=58	5 ± 7%	-11 ± 8%	10%

*Mean % of patients rated as excellent or good global improvement at endpoint (week 11).

for use of the tube gel over the jar gel was reported by 52% of patients; once daily dosing was reported as a preference by 87% of patients.

A 2-week, crossover, randomized trial (n=52) compared patient preference and cutaneous tolerability of the tube gel and jar gel formulations of BP 5%/clindamycin 1%, applied once daily and twice daily, respectively (Figure 1).[22] The tube gel was preferred by 76% of patients with several factors identified as advantages of the tube gel formulation. Such factors included ease of use, more convenient portability, lower potential for product contamination, easier storage, easier application of appropriate drug quantity, and decreased messiness with application. The last 2 factors appear to correlate with a greater potential for product waste on application, as suggested by an independent assessment of consumption of topical acne medications. Once daily application was preferred over twice daily use by 77% of patients.

In the same 2-week, crossover trial, an evaluation of skin tolerability parameters indicated that the percentage of subjects who reported worsening of erythema, burning, and pruritus did not differ between the tube and jar gel formulations.[22] A greater number of subjects reported dryness ($P<.05$), and more patients presented with peeling based on investigator assessment with the jar gel than with the tube gel ($P<0.5$).

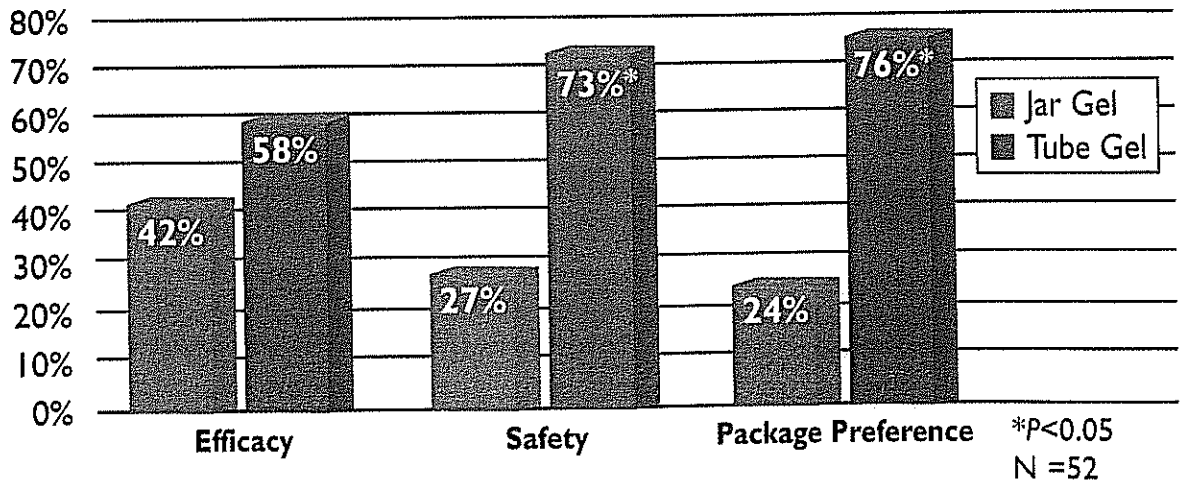
Combination Therapy Data

In a multicenter, double-blind, randomized, parallel-group, 12-week trial (n=121), tazarotene 0.1% cream applied once daily as monotherapy was compared with tazarotene 0.1 % cream applied once daily in the evening used in combination with BP 5%/clindamycin 1% tube gel applied in the morning.[23] The combination regimen achieved greater median percent reduction in comedonal lesions at week 4 (34%) and week 12 (70%) than tazarotene 0.1 % cream alone at week 4 (18%) and week 12 (60%) in subjects with moderate to severe facial acne vulgaris. Greater median percent reduction in inflammatory lesions was reported in patients with severe facial acne vulgaris for the combination regimen at week 12 (63%) versus results observed with tazarotene monotherapy (52%). The differences in these outcomes were statistically significant for both comedonal lesions ($P<.01$) and inflammatory lesions ($P<.01$).

In the above-referenced comparison study of tazarotene 0.1% cream applied once daily as monotherapy versus tazarotene 0.1% cream applied once daily in the evening combined with BP 5%/clindamycin 1% tube gel applied in the morning, there was no statistically significant difference between both groups with regard to skin tolerability. Evaluated parameters included peeling, burning, pruritus, dryness, erythema, oiliness, and irritation of facial skin. Trend analysis revealed a lower incidence of peeling and dryness in the combination regimen group. Considering the fact that the combination therapy group utilized a BP-containing formulation and a topical retinoid each day from the outset, one would anticipate that a considerable number of patients would develop signs and symptoms of facial skin intolerability, especially as compared to a monotherapy topical regimen. Additional documented cases have demonstrated efficacy and safety of BP 5%/clindamycin 1% tube gel applied in the morning and topical adapalene 0.1% gel applied once daily in the evening.[24] The emollient and humectant components of the BP 5%/clindamycin 1% tube gel formulation were suggested by the authors as major factors related to the favorable facial skin tolerability of the combination regimens.

Figures 2A and 2B demonstrate marked improvement of acne vulgaris in a 15-year-old female treated with BP 5%/clindamycin 1% tube gel applied in the morning used in combination with tazarotene 0.1% cream applied once daily in the evening. Note the reduction in both inflammatory and noninflammatory lesions after 6 weeks of use. The combination

Figure 1. Results of Patient Questionnaire Regarding Product Preference.[22]



(Adapted from Tanghetti E., et al. Poster P108 presented at 63rd Annual American Academy of Dermatology February 18-20 200b: New Orleans, LA.)

Figure 2A. Patient at Baseline.

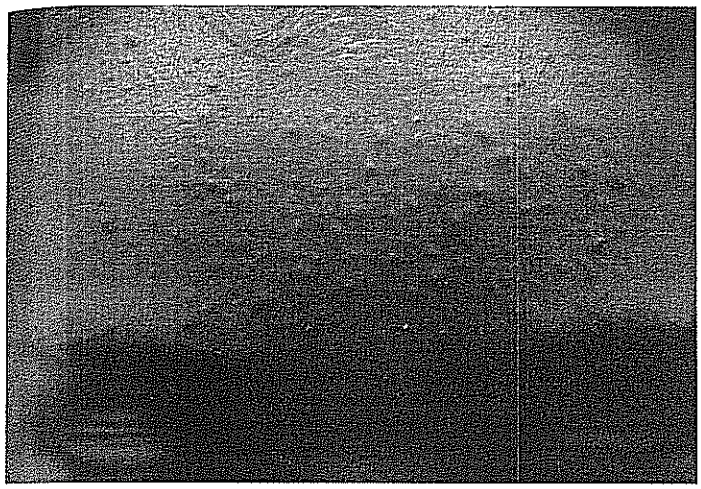
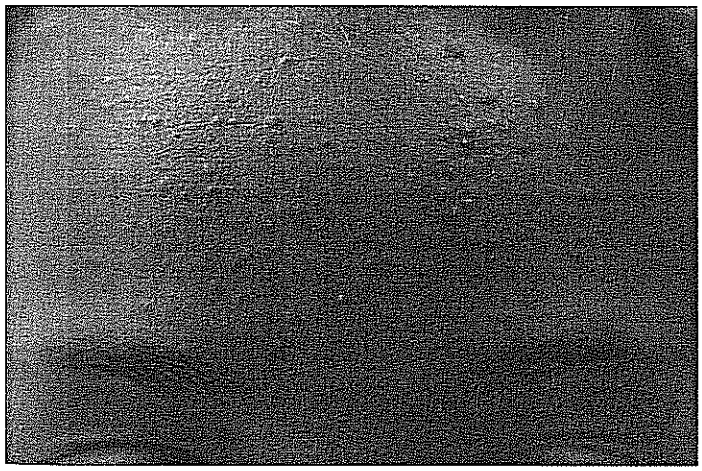


Figure 2B. Patient at 6 Weeks of BP 5%/Clindamycin 1% Tube Gel Applied in the Morning and Tazarotene 0.1 % Cream Applied in the Evening.



therapy was well-tolerated by the patient with no adverse reactions noted and no signs or symptoms of skin irritation reported.

Summary

Maintenance of epidermal barrier integrity and function are vital components of successful topical treatment of acne vulgaris. The epidermal barrier may be impaired by the intrinsic nature of the disease state, suboptimal skin care practices and certain topical medications. Use of formulations designed to minimize barrier impairment and reduce the risk of skin irritation is most likely to achieve effective results and optimize compliance with the therapeutic regimen.

The inclusion of the humectant, glycerin, and the emollient-occlusive agent, dimethicone, as components of the tube gel formulation of BP 5%/clindamycin 1% appears to be associated with improved tolerability as compared to the jar gel formulation. Overall, patient preference data indicate that most patients prefer use of the tube gel as compared to the jar gel. The combination of BP 5%/clindamycin 1% tube gel formulation applied in the morning and a topical retinoid applied in the evening has been shown to be effective and is well-tolerated in the majority of patients.

References

1. Del Rosso JQ. A qualitative and quantitative assessment of the application and consumption of topical acne medication by patients. *Cosmet Dermatol.* 2005 (in press).
2. Johnson AW. The skin moisturizer marketplace. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization.* New York, NY: Marcel Dekker; 2002:1-30.
3. Draelos ZD. Therapeutic moisturizers. *Dermatol Clin.* 2000;18:597-607.
4. Flynn TC, Petros J, Clark RE, et al. Dry skin and moisturizers. *Clin Dermatol.* 2001;19:387-392.
5. Del Rosso JQ. Understanding skin cleansers and moisturizers: the correlation of formulation science with the art of clinical use. *Cosmet Dermatol.* 2003;16:19-31.
6. Draelos ZD. Moisturizers. In: Draelos ZD, ed. *Cosmetics in Dermatology.* 2nd ed. New York, NY: Churchill-Livingstone; 1995:83-95.
7. Loden M. Role of topical emollients and moisturizers in the treatment of dry skin barrier disorders. *Am J Clin Dermatol.* 2003;4(11):771-788.
8. Rawlings AV, Harding CR, Watkinson A, Scott IR. Dry and xerotic skin conditions. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization.* New York, NY: Marcel Dekker; 2002:119-144.
9. Harding CR. The stratum corneum: structure and function in health and disease. *Dermatol Ther.* 2004;17;6-15.
10. Menon GK, Feingold KR, Elias PM. Lamellar body secretory response to barrier disruption. *J Invest Dermatol.* 1992;98:279-289.
11. Zettersten EM, Ghadially R, Feingold KR, et al. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronically aged skin. *J Am Acad Dermatol.* 1997;37:403-408.
12. Fluhr J, Holleran WM, Berardesca E. Clinical effects of emollients on skin. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization.* New York, NY: Marcel Dekker; 2002:223-243.
13. Mao-Qiang M, Brown BE, Wu-Pong S, et al. Exogenous non-physiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. *Arch Dermatol.* 1995;131:809-816.
14. Tabata N, O'Goshi K, Zhen XY, et al. Biophysical assessment of persistent effects of moisturizers after daily applications: evaluation of corneotherapy. *Dermatology.* 2000;200:308-313.
15. Subramanyan K. Role of mild cleansing in the management of patient skin. *Dermatol Ther.* 2004;17;26-34.
16. Del Rosso JQ. Adjunctive skin care in the management of rosacea: cleansers, moisturizers, and photoprotectants. *Cutis.* 2005;75(3S):17-21.

17. Rawlings AV, Harding C, Watkinson A, et al. The effect of glycerol and humidity on desmosome degradation in stratum corneum. *Arch Dermatol Res*. 1995;287:457-464.

18. Froebe CL, Simion FA, Ohlmeyer H, et al. Prevention of stratum corneum lipid phase transitions in vitro by glycerol: an alternative mechanism for skin moisturization. *J Soc Cosmet Chem*. 1990;41:51-65.

19. Nichols K, Desai N, Lebwohl MG. Effective sunscreen ingredients and cutaneous irritation in patients with rosacea. *Cutis*. 1998;61:344-346.

20. Lookingbill DP, Chalker DK, Lindholm JS, et al. Treatment of acne with a combination clindamycin/benzoyl peroxide gel compared with clindamycin gel, benzoyl peroxide gel and vehicle gel: combined results of two double blind investigations. *J Am Acad Dermatol*. 1997;37:590-595.

21. Fagundes DS, Fraser JM, Klauda HC. Difference in the irritation potential and cosmetic acceptability of two combination topical acne gels – combined results of two comparative studies. *Today's Ther Trends*. 2003;21:269-275.

22. Tanghetti EA, Gold MH, Fraser JM. A two-center patient preference study comparing two benzoyl peroxide/clindamycin gels in acne vulgaris patients (P108). Poster presented at 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.

23. Tanghetti E, Abramovits W, Solomon B, et al. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: a multicenter, double-blind, randomized, parallel-group trial (P147). Poster presented at 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.

24. Bikowski JB. Case study results of clindamycin 1%/benzoyl peroxide 5% gel as monotherapy and in combination (P118). Poster presented at 63rd Annual Meeting of the American Academy of Dermatology; February 18-22, 2005; New Orleans, LA.

Address for Correspondence

James Q. Del Rosso DO
c/o Physician Resources
28 Montclair Ave.
Montclair, NJ 07042
Phone: 973-783-4575
Fax: 973-783-4576
e-mail: doctorskin777@yahoo.com