

REVIEW ARTICLE

Contact dermatitis to topical acne drugs: a review of the literature

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ABSTRACT: Acne vulgaris is a chronic dermatological disorder that affects the majority of teenagers in the Western world. Topical therapy is widely used to treat mild-moderate acne and is known as well-tolerated thanks to its low systemic toxicity, although associated to skin adverse effects. Acne seems to be associated also to an intrinsic alteration of the epidermal barrier, regarding both the upper and the follicular stratum corneum that promotes the onset of such local side effects. The commonest one is irritant contact dermatitis, an event of frequent observation occurring with erythema, burning, dryness, scaling, and itching, usually characterized by low severity and limited duration. Among topical acne drugs, retinoids are the most irritating ones. Another side effect is allergic contact dermatitis: it is rare and mainly associated to benzoyl peroxide.

KEYWORDS: acne, allergic contact dermatitis, irritant contact dermatitis

Introduction

Acne vulgaris is a chronic dermatological disorder generally characterized by blackheads and whiteheads, pimples, scars, and greasy skin that affects 80–90% of teenagers in the Western world. Nowadays, many options are available to treat acne and to improve its appearance. Topical therapy alone is preferred for mild-moderate acne. Oral therapy is chosen for severe acne as

well as cases refractory to topical drugs or covering large areas of the body.

Topical acne drugs have to be directly applied to the skin thereby lessening the potential for internal effects and systemic drug interactions, but are not free from cutaneous side effects. This review examines all the local collateral effects of commonly available topical acne drugs.

Acne vulgaris and the epidermal barrier

Acne is an androgen-dependent disorder of pilosebaceous unit. The main pathogenetic mechanisms include increased sebum production,

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Table 1. Intrinsic functional skin barrier alterations in acne patients

Increased expression of FLG in follicular keratinocytes
Increased size of sebaceous glands
Increased secretion of sebum
Increased quantity of squalene
Decrease of free fat acids
Dilution of linoleic acid
Increased TEWL
Decreased hydration
Decrease of sphingosines and ceramids

hyperkeratinization, and occlusion of the follicular duct, follicular colonization by *Propionibacterium acnes*, and an inflammatory reaction. However, convincing evidence supports the concept that acne vulgaris is also associated with inherent abnormalities in epidermal barrier functions (1) (Table 1). Physiologically, these include homeostatic control of water content and flux (permeability barrier), recognition and neutralization of microbial organisms (antimicrobial barrier), countering of reactive oxygen species (antioxidant barrier), protection from effects of ultraviolet (UV) light exposure (photoprotection barrier), and response to exogenous allergens and haptens (immunologic barrier). Many of these barrier functions occur within the stratum corneum (SC) (2). In acne, epidermal barrier dysfunction may involve both the epidermis of the exposed skin surface and the follicular epithelial barrier, which is known to be directly involved in comedogenesis and inflammation.

Although exceptions may exist, facial skin of acne patients is characterized by higher sebum production and larger size of sebaceous glands when compared with unaffected subjects. Along with the increased sebum secretion, several qualitative modifications have been described in sebum of acne patients, first, a decreased amounts of linoleic acid (3). Depletion of linoleic acid in follicular and skin sphingolipids caused by the dilutional effect of hyperseborrhea has been hypothesized to be involved in follicular hyperkeratosis (4) as well as in impairment of the epidermal barrier function (5). The latter has been shown to predispose both to a diminished water barrier function, measured as an increase in transepidermal water loss (TEWL) and lower SC hydration (6), and to an increased permeability of comedonal wall to inflammatory substances (5). Recent studies have reported a significantly different ratio between saturated and unsaturated fatty acids constituting sebum in acne patients (7).

Moreover, postsynthetic compositional changes can occur; the accumulation of lipid peroxides, namely peroxidated squalene, seems to be responsible for the inflammatory changes in comedones (8). Taken together, these data suggest that in acne patients, modifications of the sebum composition and consequent reduced free sphingosine and total ceramides in SC impact keratinocyte proliferation and differentiation and may be responsible for both inflammatory changes in comedones and SC permeability barrier impairment.

In acne patients, alterations in epidermal barrier functions seem to be related to abnormal expression of various constitutive skin elements as well. Filaggrin (FLG) is a key protein in epidermal differentiation and contributes to the structural and functional integrity of epithelial barrier formation. Within acne lesions, there is an increase in FLG expression in keratinocytes lining the sebaceous duct and infundibulum (9). Null mutations in FLG gene have been shown to cause ichthyosis vulgaris and are a major risk factor for eczema and other atopic diseases (10). The results of a study assessing the frequency of null mutations in FLG gene in acne patients compared with matched controls failed to find significant differences (11). Consistent with this, carriage of mutations in FLG gene seems unlikely to be directly involved in acne pathomechanisms. Thus, the overexpression of FLG in the pilosebaceous units reported in acne probably reflects other alterations in keratinocyte differentiation.

A further element potentially involved in an altered epidermal barrier function in acne is represented by inflammation, which is a pivotal pathogenic factor of this disease. The normal-appearing facial skin of patients with acne exhibits specific perifollicular and follicular patterns of inflammatory cellular infiltration and inflammatory marker expression, suggesting that subclinical inflammation exists in acne prone areas (12). Loss of physical barrier integrity sometimes occurs when the intensity of inflammation reduces the strength of the follicular wall. In inflammatory acne lesions, this can even lead to various degrees of follicular rupture. *P. acnes* has a strong proinflammatory activity as it activates several inflammatory cascades related to innate, acquired, and humoral immunological responses (13). *P. acnes* itself secretes lipases, proteinases, chemotactic factors, and proinflammatory cytokines (13); moreover, *P. acnes* can enhance expression of antimicrobial peptides in sebocytes and keratinocytes (13). Lastly, *P. acnes* catalytic

Table 2. Functional skin barrier alterations caused by topical acne drugs

BP	Topical retinoids
Increased TEWL	Decrease of SC thickness
Decrease of epidermal antioxidants	Altered expression of TLR-2
	Decreased degradation of dermal matrix
	Altered desmosomes in the spinous layer
	Decreased quantity of tonofilamentis

breakdown products, after being released into the dermis, may intensify the inflammatory process by their antigenic, enzymatic complement activation, and chemoattractant activities (14).

Adverse effects to anti-acne drugs

Irritant contact dermatitis

Irritant contact dermatitis (ICD) to topical acne drugs is an event of rather frequent observation, as it emerges from the data of the literature (15,16) and from the daily experience of dermatologists and patients. However, this “obliged” adverse effect is characterized by a low severity and of limited duration. ICD in acneic patients is mainly caused by two different factors: first, the intrinsic alteration of the epidermal barrier in this particular class of patients, which adds to the further alteration induced by topical acne drugs. Moreover, every topical acne drug is potentially irritating because of its intrinsic mechanism of action (Table 2).

Topical retinoids. Among over 5000 identified or synthesized retinoids, nowadays, only four are topically used: tretinoin, isotretinoin, adapalene, and tazarotene. Even if these retinoids are the most effective antiblackhead topical drugs, the main drawback is local irritation that happens in every patient using them. Topical retinoids alter the expression of the toll-like receptor 2 (TLR2) and reduce the thickness of the SC (probably through an enhanced cellular turnover) resulting in an alteration of the skin barrier permeability and a reduction of the dermal matrix degradation induced by chronic photodamage (1,17). Moreover, they cause alterations of desmosomes and reduction of tonofilaments in the spinous layer (18).

Tretinoin (all-trans retinoic acid), used at a concentration of 0.05–0.1% in various galenic

formulations, is the most irritating retinoid. A lower concentration (0.025%), gel formulations containing polyol prepolymer-2, and formulations in microgranules (10–25 nm diameter) with high porosity seem to be less irritating (19).

Isotretinoin is used at a concentration of 0.05% in cream or gel and is characterized by a lower irritating potential compared with tretinoin (19). Both tretinoin and isotretinoin are better tolerated once mixed with UV-filters (20).

Tazarotene, used at a concentration of 0.05–0.1%, has an irritating potential similar to tretinoin (19) and seems to be the worst tolerated retinoid: skin irritation was reported in 50% of the patients applying tazarotene once daily and rinsing it off after 2–10 minutes (21); moreover, the use of tazarotene is related to increased risk of sunburn, hence, UV protection is highly recommended.

Among the aforementioned retinoids, the less irritating is adapalene. It is a third generation retinoid that is used at a concentration of 0.1% in cream or gel.

Benzoyl peroxide. Benzoyl peroxide (BP) is a topical acne drug with bactericidal effect on *P. acnes*. It does not induce antibiotic resistance and is associated to common adverse effects, such as dryness, erythema, and scaling. They are less frequent at a concentration of 2–5%, rather than 10%, and with cream or lotion formulations compared with gel. What is more, BP commonly causes brightening of hair and garments (19).

Topical antibacterials. The main benefit of topical antibiotics (tetracyclines, erythromycin, clindamycin) is their low irritating potential. Anyway, their prolonged application may induce antibiotic resistance.

Miscellany. Salicylic acid at a concentration of 2% is associated to common adverse effects as scaling and burning. Topical sulfur rarely causes adverse reactions, such as dryness and/or bad odor. Also, sodium sulfacetamide is characterized by rare adverse effects, usually restricted to itching and erythema. Azelaic acid is commonly associated to itching, burning, and dysesthesia (22).

Prevention. Topical acne drugs cause adverse effects regardless of their therapeutic efficacy. For this reason, it is advisable to “educate” patients so that they can reduce as much as possible the onset risk or the severity of ICD (22).

First of all, the role of general principles as quantity, frequency, and duration of application must be emphasized. The quantity of topical acne drugs that should be applied on the face is 0.6 g, usually once daily, rinsing it off after 8–12 hours. Conversely, cleansers and masks containing salicylic acid, BP, sulfur, and/or sodium sulfacetamide have to be rinsed off after few minutes. The risk of ICD should be established for every patient basing on the skin type. Sensitive and dry skin show a greater tendency to irritation, as well as skin of people with positive history for eczematous dermatitis, atopic dermatitis, and xerosis. Moreover, risk of ICD to topical acne drugs is increased in cases of repeated daily washing of the face or rubbing by sponges or similar products.

Allergic contact dermatitis

Allergic contact dermatitis (ACD) from topical products is an uncommon but probably underdiagnosed event during the treatment of patients affected by acne vulgaris. ACD, a type IV hypersensitivity reaction, should be suspected when patients complain of worsening of their dermatitis or acutely develop pruritic, erythematous, edematous papules, and vesicles at the sites of application of the various products. Furthermore, as patients are often warned that many acne medicaments may be irritant, they often believe that early signs of ACD are attributable to an irritant effect and continue to apply the topical products worsening the disease. The cutaneous reaction is usually limited to the sites of application, but in a few cases, contact dermatitis may spread to other near sites (neck, upper trunk) or even give a widespread “id reaction” due to the absorption of the causative allergen.

An Italian study showed that performing patch tests in consecutive acne patients with a series of selected allergens, 3.4% of patients experienced a relevant positive patch test to topical medicaments suggesting that contact sensitization is not unusual (23). All patients developed eczematous reactions many weeks after starting the therapy and the reactions were often misinterpreted as ICD or spontaneous worsening of acne vulgaris. Spironolactone was found to be the commonest sensitizer while no positive reactions were detected from clindamycin and erythromycin.

Topical retinoids. Topical retinoids are very rare sensitizers; among the sporadic cases reported in

the literature, only a few concerned sensitization to retinoic acid in acne patients (23,24). Tomb et al. described a case of contact allergy in a patient with positive patch tests to tretinoin and isotretinoin (25). No cases of allergy to adapalene are described in the literature except a case of contact dermatitis due to a gel containing both adapalene and BP (26).

Systemic retinoids assumed for severe cystic acne were found to predispose to contact sensitization (27). Oral isotretinoin may affect the function and structure of the epidermis inhibiting sebum production, causing loss of tonofilaments, and increasing epidermal fragility; a thinner SC and a consequent damaged barrier function allow a greater antigen penetration. Furthermore, retinoids increase the density of Langerhans cells, the antigen-presenting cells in the sensitization phase of ACD, enhancing immune-responsiveness against antigens. Patients using systemic retinoids usually apply numerous emollients and cosmetics to control cutaneous xerosis. All these factors may promote sensitization to allergens in topical products as well as other common environmental contact antigens like metals (27).

Benzoyl peroxide. BP is one of the widest medical prescriptions for acne patients but is also available in many over the counter products. The allergenic properties of this molecule were clearly evidenced in the past in patients affected by acne vulgaris (28) as well as chronic leg ulcers or stasis dermatitis of the lower legs (28,29).

Lindemayr and Drobil, patch testing 59 patients affected by acne vulgaris with BP 5% found three positive reactions (5.1%) (30), while Balato et al. testing with BP 2% found two (1%) true allergic reactions (23). Allergic reactions developed after long course of topical use of BP (mean 10.7 months) (30). In a retrospective study performed in a large cohort of patients submitted to patch tests with BP 1%, weak positive reactions occurred in 6.5% of cases, and strong positive reactions in 1.3% revealing that allergy to BP is not unusual (31). Young individuals had more positive reactions to BP than older people and patients with face dermatitis had an increased risk of sensitization; however, the certain connection with previous acne treatments could not be drawn concretely as the diagnosis of acne had not been registered in the enrolment files.

Revising the literature, some case reports underline unexpected clinical pattern of ACD from BP. Florid aspects or an unusual, probably

Table 3. Cutaneous side effects of topical acne drugs

Drug	Erythema	Scaling	Dryness	Burning/ Itching	Phototoxicity	Other
Tretinoin	+++	+++	+++	++	++	
Isotretinoin	++	++	++	+	+	
Adapalene	+	+	+	+	+	
Tazarotene	+++	+++	+++	++	++	
Benzoyl peroxide	++	++	++	+	–	ACD*, hair and garments brightening
Clindamycin	±	–	±	±	–	ACD*
Erythromycin	±	±	±	–	–	ACD*
Salicylic acid	–	±	–	±	–	
Sulfur	–	–	±	–	–	Bad odor
Sodium sulfacetamide	±	–	–	±	–	
Azelaic acid	–	–	–	+	–	

*ACD, allergic contact dermatitis.

Scale from –, ±, +, ++, +++.

underreported, angioedematous aspect, without other typical signs of contact dermatitis were noticed (32–34); a purpuric ACD has been reported as well (35). In patients previously strongly sensitized to BP during earlier acne treatments, ACD may occur as a consort dermatitis being later transferred from a husband or from an affectionate son to mother via direct contact to facial skin (36).

Topical antibiotics. The overall prevalence of ACD to topical antibiotics is generally low (37). The aminoglycosides are recognized as the most common antibiotic molecules responsible for contact sensitization in general population. Current guidelines for acne vulgaris management do not recommend aminoglycosides but only consider clindamycin and erythromycin (38). Both these antibiotics are known as weak contact allergens; however, their prolonged use on a previously irritated and impaired barrier like that of acne patients could easily explain the cases of sensitization reported in the literature. Clindamycin has been used to treat acne since 1976 and the first cases of contact sensitization were reported in 1978 (39), followed by other few cases in acne (40) or other pathologies (41). A case of cross reaction between clindamycin and the structurally related lincosamide lincomycin was reported in a patient exposed both to topical and systemic clindamycin; clindamycin hydrochloride 0.5% and 1% aq. and clindamycin phosphate 0.1% and 1% aq. were the concentrations used for patch testing (42).

The macrolide erythromycin, due to its high molecular weight and its structural formula has

a low sensitization potential. ACD from erythromycin was exceptionally observed and especially in pathologies other than acne (43).

Miscellany. Spironolactone, a synthetic steroid derivative of 17-spirolactone with antiandrogenic effects, at the moment is no more used as not included in current guidelines (38). However, this molecule showed allergenic properties and was found to be responsible for few cases of ACD in the past (44). The 1% pet. concentration seems the advisable patch-test concentration to avoid irritant reactions (44).

Other cutaneous adverse effects

Apart from contact dermatitis, topical products used for acne may rarely determine other cutaneous reactions. The phototoxic potential of BP has been demonstrated but seldom reported on clinical case series (45,46). The ultraviolet (UV)B phototoxicity was found in eight patients (33%) on repeatedly irradiated areas, while no UVA phototoxicity was evidenced, confirming the possible phototoxic action of BP after UVB exposure.

BP may seldom be implicated in cases of immunological immediate contact urticaria (47). This reaction must be suspected in patients previously sensitized to the drug who develop immediate itching, erythema, edema, or wheals in the sites of application of the medicament. The reaction is usually limited to the sites of application but sometimes, especially, in atopic subjects or strongly sensitized individuals, may spread to other sites with eventual systemic symptoms.

Conclusion

Local collateral effects to topical acne drugs are commonplace regardless of their therapeutic efficacy.

When prescribing topical treatments for acne, physicians should be aware of a variable impairment of the cutaneous barrier function consequent to abnormalities in epidermal constituents and sebum composition as well as to inflammation, even subclinical. In fact, one of the major limitations of topical therapies for acne, especially for facial acne, is the relatively high irritancy. These reactions can result from direct effects of active principles and/or the characteristics of the vehicle, but also from a defect in skin barrier function. This may lead the patients to elect treatment discontinuation, which usually results in less than optimal therapeutic outcomes.

Physicians have to keep in mind that ICD to topical acne drugs is the commonest adverse effect and ACD is rare but possible, in particular to BP (Table 3). In view of the rarity of these latter reactions, a specific patch-test series does not seem to be required, while performing patch test with patient's own products is usually enough to diagnosis.

Conflict of interest

None.

Financial support

None.

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