

Role of topical combination drug containing clindamycin and benzoyl peroxide in the treatment of common acne

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Abstract

Common acne is a very frequent disorder of sebaceous glands which affects mainly young people. In the majority of patients (85%) acne is mild to moderate, and amenable to topical therapy. According to the European Evidence-based (S3) Guidelines for the Treatment of Acne, therapy of comedonal acne should begin with topical retinoids (preferably adapalene), while mild to moderate cases of papulopustular acne should be initially treated with combination drugs (clindamycin + benzoyl peroxide or adapalene + benzoyl peroxide). It needs to be stressed that all of the above-mentioned combination drugs demonstrate similar efficacy in terms of reducing the number of skin lesions, both inflammatory and non-inflammatory. The onset of therapeutic effect, however, has been shown to be significantly more rapid with the clindamycin + benzoyl peroxide combination. Moreover, the combination is much better tolerated by patients than adapalene + benzoyl peroxide, and has a greater safety profile, as demonstrated in a clinical trial involving a total of 382 patients suffering from common acne. The present article discusses the properties of individual components of the combination drugs listed above, and compares both combinations in terms of their therapeutic efficacy, tolerability and safety.

Key words: acne, combination drugs, benzoyl peroxide, adapalene, clindamycin.

Introduction

Common acne (juvenile acne, *acne vulgaris*) is a chronic inflammatory disease of sebaceous glands and hair follicle orifices (so-called pilosebaceous units), which involves the formation of both non-inflamed (microcomedones, open and closed comedones) and inflamed (papules, pustules, cysts) skin lesions [1, 2]. It is the most common skin disease occurring in puberty. It affects up to 80-100% people between 11 and 30 years of age. Eighty five percent of all cases are mild in character (comedonal acne or papulopustular acne of low severity) [3-5].

The etiopathogenesis of acne is a complex and multifactorial process. The condition is believed to develop as a result of interplay of the following factors:

- increased activity of sebaceous glands [6, 7],
- hyperkeratosis of the epithelium in follicular openings leading to their blockage and the formation of microcomedones [8-10],
- colonization of sebaceous ducts by *Propionibacterium acnes*, triggering inflammation through the activation of toll-like receptors (TLRs) on the surface of inflamma-

tory cells [11, 12]; it should be noted that according to contemporary views on the etiopathogenesis of acne inflammatory processes precede hyperkeratosis of sebaceous gland openings;

- induction of inflammatory changes through the activated cascade of proinflammatory cytokines [13].

The clinical picture of acne is very diverse (Fig. 1). Skin lesions begin with the formation of a microcomedo in a pilosebaceous unit. The microcomedo may subsequently turn into a clinical form of comedo, followed by a papule and then pustule. More severe forms of the disease involve the development of cysts, nodular infiltrations and, as a consequence, unsightly and even disfiguring scars and discolorations. Acne lesions are typically located in the face (99% of all cases), followed by the back (60%) and chest (15%) [14].

General rules of acne therapy

In order to optimize acne treatment, some general recommendations should be observed. Common acne therapy should begin as early as possible to avoid post-acne

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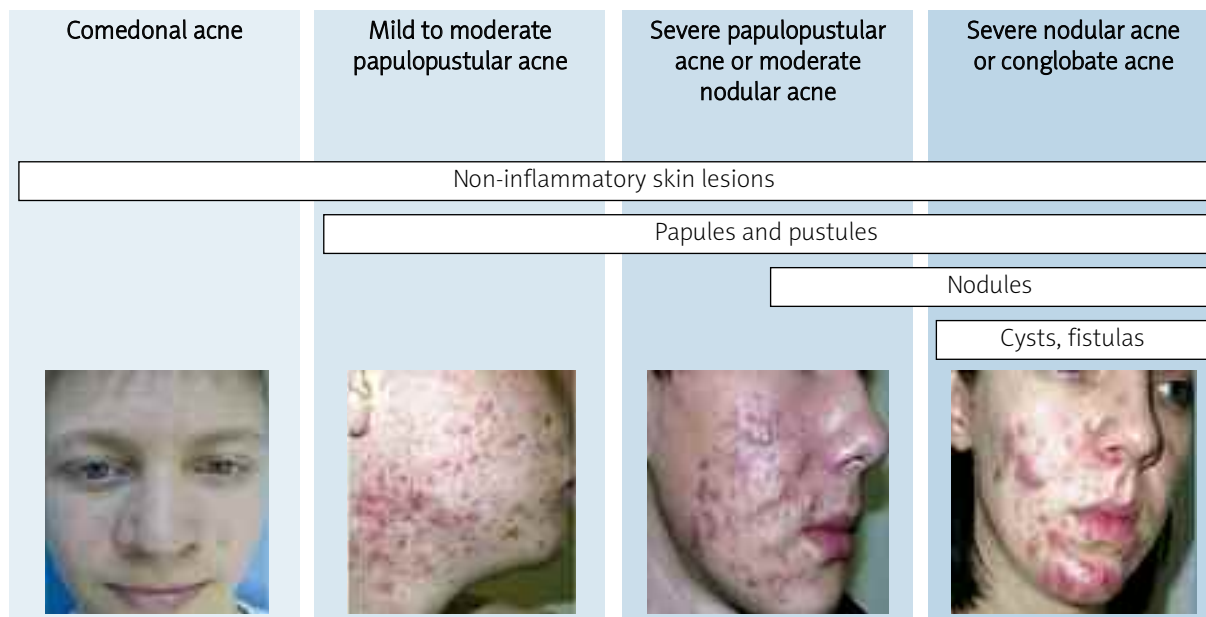


Figure 1. Clinical classification of common acne

complications (cysts, scarring or post-inflammatory discolorations) [15]. Treatment must be individualized on the basis of severity, clinical manifestations and progression of the disease, and should take into account high-quality scientific evidence (preferably consensus-based guidelines established by renowned experts in the field) [16]. Good therapeutic effects, however, are not only dependent on well selected drugs, but also on appropriate cooperation between the patient and the physician. Since acne therapy is a prolonged process, prior to the initiation of treatment dermatologists should inform their patients of the fact that it may take up to several months to achieve a successful outcome. During the first month of therapy, local improvement is only seen in a small proportion of patients. At the end of the third month of treatment, however, improvement can be noticed in ca. 60-70% of patients [17]. Also, the patient's attention must be drawn to the correct method of application of topical preparations. Instead of individual acne eruptions, they should be applied over the entire sebaceous area.

Role of topical combination drugs in the treatment of common acne

Topical treatment is the cornerstone of treatment of comedonal acne and papulopustular acne of mild to moderate severity. According to the European Evidence-based (S3) Guidelines for the Treatment of Acne, therapy of mild to moderate comedonal acne should begin with topical retinoids (adapalene being the preferred option due to the best tolerance and greatest safety profile), while mild to moderate cases of papulopustular acne should be

initially treated with combination drugs (clindamycin + benzoyl peroxide or adapalene + benzoyl peroxide). Both combined drugs demonstrate similar efficacy in terms of reducing the number of both inflammatory and non-inflammatory skin lesions. The former combination (clindamycin + benzoyl peroxide), however, leads to a significantly more rapid clinical improvement and has a better safety profile, as shown in a multi-centre clinical trial [18].

It is worthwhile to note that there are three types of evidence-based guidelines (types S1-S3). S1 guidelines are established on the basis of an informal consensus of an expert group. S2 guidelines emerge from a formal consensus process conducted among a selected group of experts. S3 guidelines are developed on the basis of a consensus stemming from a review of medical reports accompanied by an evaluation of their scientific value. The European Evidence-based Guidelines for the Treatment of Acne published in 2011 are S3-type guidelines, i.e. the most reliable source of knowledge. All the therapeutic recommendations included in the Guidelines have a defined strength of recommendation (high, medium, low), depending on how well they are documented (Table 1).

As already mentioned above, the mainstay of therapy for patients with mild to moderate papulopustular acne are combination drugs (high strength of recommendation according to the S3 Guidelines). The preparations, which represent the latest advance in acne therapy, carry multiple benefits including:

- high efficacy (reduction of the number of both inflammatory and non-inflammatory lesions, more rapid regression of skin eruptions and shorter duration of treatment compared to monotherapy); due to their

Table 1. An excerpt from the acne treatment algorithm (including recommendations of high and medium strength) according to the European Evidence-based (S3) Guidelines for the Treatment of Acne

Strength of recommendation	Comedonal acne	Mild to moderate papulopustular acne	Severe papulopustular acne or moderate nodular acne	Severe nodular acne or conglobate acne
I*	–	Adapalene + BPO or BPO + clindamycin	Isotretinoin	Isotretinoin
II**	Topical retinoid	Azelaic acid or BPO or topical retinoid or systemic antibiotic + adapalene	Systemic antibiotic + adapalene or systemic antibiotic + azelaic acid or systemic antibiotic + adapalene + BPO	Systemic antibiotic + azelaic acid

*I – high strength of recommendation according to the European Evidence-based (S3) Guidelines (based on at least two double-blind randomized controlled clinical trials with no errors in design), **II – medium strength of recommendation according to the European Evidence-based (S3) Guidelines (based on at least three double-blind randomized controlled clinical trials, though of lower quality than in I*)

composition (based on components with diverse mechanisms of action and different target points which, in addition to complementing each other, produce a synergistic effect) combination drugs effectively target the main pathophysiological factors of acne: clindamycin has bactericidal, inflammatory and weak comedolytic properties [19], benzoyl peroxide is a bactericidal, exfoliative and mild anti-inflammatory agent [20], while retinoids are highly effective anti-comedogenic and comedolytic substances which, by modulating immune response and affecting inflammatory mediators and migration of inflammatory cells, also exhibit anti-inflammatory action [21, 22];

- safety of use – importantly, the application of combination drugs reduces the risk of development of antibiotic-resistant bacteria [23];
- relatively good tolerance profile, as long as all the instructions given by the physician are followed (avoidance of excessive UV exposure during therapy, application of a thin film of the preparations to clean dry skin avoiding the eye and mouth area);
- lack of concerns about the stability and chemical compatibility of using two separate preparations;
- easy application (once daily) improving cooperation between the physician and the patient.

Properties of individual components of combination drugs under discussion

Clindamycin is a lincosamide antibiotic. It has a primarily antibacterial (bactericidal and bacteriostatic) effect. Clindamycin reduces the *P. acnes* count both on the surface of the skin and in sebaceous gland ducts. Furthermore, it relieves local inflammation by inhibiting the chemotaxis of polynuclear granulocytes, and reduces by up to 50% the levels of free fatty acids on the skin sur-

face. The keratolytic effect of clindamycin, on the other hand, is weak (Table 2) [24].

Clindamycin is generally very well tolerated by patients. Adverse effects associated with clindamycin therapy, including allergic and phototoxic reactions, are rare (Table 3). Used in monotherapy, however, clindamycin tends to lead to the development of antibiotic resistance both in *P. acnes* and other bacteria (the risk also applies to other topical and systemic antibiotics used in acne therapy).

Benzoyl peroxide is primarily a bactericidal agent. The decomposition of benzoyl peroxide releases oxygen as a by-product. The oxygen suppresses the growth of anaerobic bacteria *P. acnes*. By hindering bacterial colonization in sebaceous ducts, oxygen markedly reduces bacterial count (even by over 95% during 2 weeks) [25]. Through the inhibition of *P. acnes* growth benzoyl peroxide also decreases the production of free fatty acids by the bacteria [26]. It also has keratolytic (exfoliative) properties, substantially reducing the number of both closed and open comedones. In addition, it has some anti-inflammatory properties (manifested as a reduction in the number of papules and pustules) and blocks excessive sebum production (Table 2). It should be pointed out that due to its specific mechanism of action no resistance to benzoyl peroxide is observed. If higher concentrations of benzoyl peroxide are used, the incidence and severity of adverse reactions (dry exfoliating skin and inflammatory skin reaction) may be increased (Table 3). Also, the drug should not be applied on the neck and sensitive areas in the face (around the mouth, eyes and nose). Benzoyl peroxide may have a bleaching effect on hair and clothes. Application of the combination with the antibiotic ensures its better tolerance (clinical observations).

Table 2. Efficacy of preparations applied topically for acne treatment

Preparations	Comedolytic effect	Antibacterial effect	Anti-inflammatory effect
Topical antibiotics			
Clindamycin	(+)	++	+
Antibacterial preparation			
BPO	+	+++	(+)
Combination drug			
Clindamycin + BPO	+	+++	+
Retinoids			
Tretinoin	++	-	-
Isotretinoin	++	-	(+)
Adapalene	++	-	+
Tazarotene	++	-	(+)
Others			
Azelaic acid	+	-	(+)

BPO – benzoyl peroxide, +++ very strong, ++ strong, + moderate, (+) mild, – none

Adapalene is a third-generation topical retinoid, a synthetic naphthoic acid derivative. Similarly to tretinoin, it binds to retinoic acid receptors. Also, it exhibits a special affinity for epithelial retinoic acid receptors RAR- γ (tretinoin has identical affinity for RAR- α , RAR- β and RAR- γ) [27]. Adapalene blocks the activity of polynuclear leukocytes (it is a potent inhibitor of the activity of neutrophil lipoxigenase) and immune responses mediated by arachidonic acid (preventing the development of leukotriene-dependent inflammatory mechanisms) [28]. It blocks the migration of leukocytes and the synthesis of prostaglandin E2. Furthermore, as mentioned above, it induces a dose-dependent inhibition of receptors TLR-2 in human lymphocyte cultures (via these receptors *P. acnes* bacteria trigger the production of proinflammatory cytokines) and blocks the inflammatory pathway AP-1.

Tenaud *et al.* have also shown that by affecting these receptors adapalene increases the expression of CD-1d molecules and, at the same time, decreases the expression of IL-10 on keratinocytes. Theoretically, the process may enhance interactions between dendritic cells and T cells, thus boosting the antibacterial activity against *P. acnes*. What is more, it is a powerful inhibitor of the proliferation and differentiation of keratinocytes, which normalizes processes involved in epithelial keratosis (Table 2). It has no antiseborrheic action, though. Thanks to its ring-like structure adapalene is resistant to the effect of light and oxidative factors (excessive exposure to the sun during therapy should nevertheless be avoided) [29].

The most common adverse reactions occurring during adapalene treatment include symptoms of skin irritation: dryness, skin peeling and redness (Table 3).

Table 3. Most common adverse reactions caused by drugs applied topically for acne treatment

Preparation	Erythema	Peeling	Stinging/burning	Antibiotic resistance
Clindamycin	-	-	-	+++
BPO	++	++	+	-
Clindamycin + BPO	+	+	-	(+)
Tretinoin	+++	+++	++	-
Isotretinoin	++	++	+	-
Adapalene	+ / +++	+	+	-
Tazarotene	+++	+++	++	-
Azelaic acid	+	+	+ / ++	-

BPO – benzoyl peroxide, +++ very strong, ++ strong, + moderate, (+) mild, – none

Because of proven teratogenic effects of systemic retinoids, topical derivatives of vitamin A acid are also contraindicated during pregnancy.

Comparison of efficacy, tolerability and safety of combination drugs containing clindamycin + benzoyl peroxide and adapalene + benzoyl peroxide

The efficacy of combination drugs enumerated above was assessed in a prospective, randomized, blind, multi-centre clinical trial in which a total of 382 patients with common acne had been enrolled. All the subjects suffered from papulopustular acne and had 25-80 inflammatory skin lesions and 12-100 non-inflammatory lesions. They were divided into two study groups. The sub-group treated with a combination drug containing clindamycin + benzoyl peroxide had a total of 190 patients, while the sub-group using adapalene + benzoyl peroxide had 192 patients. The two drugs under study were applied once daily, in the evening, to carefully cleansed skin, for an overall period of 12 weeks [30].

Following final patient assessment several variables were compared:

- percentage reduction of the number of inflammatory lesions on the face (primary endpoint);
- percentage reduction of the number of non-inflammatory lesions and all acne lesions (both inflammatory and non-inflammatory);
- percentage of patients in whom a successful therapeutic outcome was recorded, defined as an improvement of at least 2 points (compared to baseline) in the 6-point ISGA (*Investigator's Static Global Assessment*) scale in which 0 represents "clear skin" with no lesions, either inflammatory or non-inflammatory, while 5 stands for severe acne with multiple inflammatory and non-inflammatory skin eruptions including nodules;
- time required to achieve a successful therapeutic outcome;
- time required to achieve a 50 percent reduction in total acne lesion count, and in the number of inflammatory and non-inflammatory lesions separately.

Tolerability was assessed in a 5-point scale encompassing erythema, dryness, peeling, pruritus and burning/stinging sensation. Safety was evaluated by monitoring adverse events.

The clinical trial outlined above demonstrated the two combination drugs to have comparable efficacy in terms of reducing inflammatory and non-inflammatory lesion counts. At 12 weeks into therapy the mean reduction of inflammatory and non-inflammatory lesions achieved with clindamycin + BPO was 76.8% and 62.2%, respectively, and with the adapalene + benzoyl peroxide combination – 72.2% and 61.5%, respectively. Consequently, it should be noted that clindamycin + BPO provided a greater reduction of inflammatory lesions than adapalene + BPO, though the differences were not statistically

significant. The reduction of non-inflammatory lesion count was comparable for both therapies (despite the fact that adapalene used in monotherapy has much stronger comedolytic properties than clindamycin or BPO). Some parameters, though, seem to suggest that the clindamycin + benzoyl peroxide combination is a superior treatment regimen. For example, according to the ISGA scale time required to achieve a successful therapeutic outcome was significantly shorter in the group of patients treated with clindamycin + benzoyl peroxide than adapalene + benzoyl peroxide. In the 4th week of therapy the overall reduction in the number of acne lesions was 63.9% among patients treated with clindamycin + BPO and 58.0% among patients using adapalene + BPO (the difference being statistically significant). Clinical improvement after using the two drugs occurs quite rapidly: a significant reduction in the number of acne lesions (inflammatory eruptions in particular) is observed during the first 2 weeks from the onset of therapy. The majority of patients – both in the group treated with adapalene + benzoyl peroxide and clindamycin + benzoyl peroxide – experience no skin irritation, or only minor symptoms of irritation. Skin irritation is nevertheless significantly more common in patients using a combination drug with a retinoid. Adverse drug reactions were reported by 48.4% patients treated with clindamycin + BPO and 78.6% of patients using adapalene + BPO. Better tolerability and safety profile of the combination drug containing clindamycin and benzoyl peroxide translate into better cooperation between the patient and the physician. Patients in the adapalene + benzoyl peroxide group tended to skip the application of the drug more frequently because of its poorer tolerability.

Prevention of antibiotic resistance with combination drugs

The issue of antibiotic resistance emerging during acne therapy has led to much concern and must therefore be addressed in greater detail. Resistance develops as a consequence of selective activity against bacteria. It may be manifested as lack of improvement or inadequate clinical response to treatment. When prescribing systemic or topical antibiotic treatment to acne patients physicians should be aware that resistance may be induced by antibiotics administered via both routes. Systemic antibiotic therapy may lead to the development of resistance in the commensal flora in all body regions, while topical treatment may cause resistance that is largely confined to the antibiotic-treated skin area [31]. There is also a risk of transmission of resistant strains between patients (e.g. siblings) and between patients and the physician [32]. Significantly, drug resistance can also spread to other pathogens on the skin (especially *Staphylococcus epidermidis*, *S. aureus* or *Streptococcus haemolyticus*)

[33, 34]. Antibiotic-resistant *P. acnes* bacteria are in fact identified in a large proportion of acne patients still before the initiation of treatment. Antibiotic resistance of *P. acnes* varies between countries and may be difficult to predict. For example, the highest resistance to clindamycin and erythromycin is found in Spain and to tetracycline – in the UK [35]. The relationship between antibiotic resistance and results of acne treatment is probably more complex than in other bacteria-caused diseases. Some clinical trials point to a reduced efficacy of erythromycin in topical acne therapy, which is likely to result from the presence of resistant strains of *P. acnes*. Over the last decades, however, there has been no evidence for impaired efficacy of systemic tetracycline or topical clindamycin therapy [36]. On the other hand, there have been a growing number of reports about infections caused by *P. acnes*, comprising arthritis, endocarditis, panophthalmitis or lymphadenitis. The incidence of infections triggered by *P. acnes* (other than acne) is, however, difficult to estimate because for a long time the bacteria were regarded as a contaminating rather than pathogenic factor. Some scientists consider *P. acnes* to be an “underestimated pathogen” [37].

In order to reduce the development of bacterial resistance to antibiotics (both topical and systemic), antibiotic monotherapy should be avoided. Topical antibiotics should, preferably, be combined with other agents such as benzoyl peroxide either in the form of combination drugs or alternate treatment. Combined use markedly reduces the risk of antibiotic resistance, which is why it is recommended in the European Evidence-based Guidelines. The duration of antibiotic therapy should be appropriately adjusted. Clinical response and the need for further treatment should be assessed between 6 and 12 weeks into therapy [18].

Conclusions

The European Evidence-based Guidelines for the Treatment of Acne recommend topical retinoids for the treatment of comedonal acne and combination drugs (clindamycin + benzoyl peroxide or adapalene + benzoyl peroxide) for the therapy of mild to moderate papulopustular acne. The two combination drugs exhibit similar efficacy. The clindamycin + benzoyl peroxide combination, however, has better tolerability and safety profile.

In view of the risk of antibiotic resistance, physicians should be very careful in prescribing both systemic and topical acne therapy. Topical antibiotics should not be used in monotherapy but in combination, e.g. with benzoyl peroxide.

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