An innovative approach to the topical treatment of acne

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Abstract: Acne is characterized by primary lesions on the face, chest, and back, and by a variety of other signs and symptoms. In particular, acne inflammatory lesions result from Propionibacterium acnes colonization and are of particular relevance as they can cause permanent scarring. Acne also causes significant psychological morbidity in affected patients. Products currently available for the treatment of acne include systemic and topical treatments. As these products can cause severe side effects, new, innovative therapies are needed. Farmaka Acne Cream (FAC) is a novel, film-forming cream developed to treat mild and moderate acne. In vitro studies have demonstrated that FAC is as effective as 5% benzoyl peroxide in inhibiting growth of P. acnes. In 32 subjects with mild or moderate acne, FAC reduced all the major signs and symptoms of the disease. These included itching, erythema, and scaling, as well as reductions in the numbers of papules, pustules, and open and closed comedones. Acne severity improved in 38% of subjects, while none worsened. FAC was found to be effective in controlling sebum secretion, and was non-comedogenic. Most subjects (90%) reported tolerability as good or very good, while clinical efficacy and cosmetic acceptability were judged as good. For assessment of contact sensitization and photosensitization, FAC was applied daily to the backs of 29 subjects in two symmetric areas for 10 days. Using a solar stimulator, one minimal erythema dose was delivered to one side of the back from days 11 to 13. The four different subareas of treated/unreated and irradiated/nonirradiated and combinations thereof were compared. No cases of contact sensitization or photosensitization were observed, and FAC is considered safe for use in intense sunlight. In vitro and in vivo studies provide evidence for the safety and clinical benefits of FAC, a promising candidate for the treatment of mild and moderate acne.

Keywords: acne, Farmaka Acne Cream, Propionibacterium acnes

Introduction

Acne is characterized by primary lesions on the face, chest, and back, which form when the skin pores become clogged with oil, dead skin cells, and bacteria. Such lesions are either noninflammatory (open and closed comedones, also called whiteheads and blackheads) or inflammatory (papules and pustules). The inflammatory manifestations of acne result from Propionibacterium acnes colonization, and are of particular relevance as they can develop into nodules and cysts, potentially leading to permanent scarring. Acne severity is classified according to different scales. It is widely agreed, however, that the mild and moderate forms of acne display primary lesions only, while severe acne also includes nodules, cysts, and eventually open lesions. It is noteworthy that acne severity and scarring have been related to P. acnes inflammatory factors, bacterial growth metabolites such as allergens, toxins, or porphyrins, and enzymes.
Acne is always accompanied by a variety of other signs and symptoms such as erythema, desquamation, burning, itching, dyschromia, and pain. Furthermore, acne causes significant psychological morbidity in affected patients.6

Acne is the most common skin disease, and although it usually manifests during puberty and worsens throughout adolescence, epidemiological studies suggest that it can arise at any age. Acne most frequently affects individuals between puberty and 30 years of age, with 79%–95% of subjects aged between 16 years and 18 years2 and 80% of subjects between puberty and 30 years of age.4 Acne is also reported in younger children, with 28%–61% of children aged between 10 years and 12 years being affected.9 The condition has even been reported in children as young as 4–7 years.10–12 The exact cause of acne is still unknown, and although early P. acnes colonization has an important role in the disease, the triggers of acne and the effect of treatment on the course of the disease remain unclear.4 Four contributing pathogenic factors of acne have, however, been clearly identified: P. acnes colonization of the pilosebaceous unit, inflammation, seborrhea, and follicular desquamation (hyperkeratosis).13 Secondary factors that could trigger or exacerbate acne may include, among others, inappropriate personal hygiene (use of abrasive soaps, harsh detergents, and excessive scrubbing), use of cosmetics and emollients (pore occlusion could cause an acneiform eruption), environmental factors (exposure to dust, dirt, polluting elements, food residues, and sweat),11,14–16 high body mass index,17,18 and common medications.19 The skin’s acid mantle is fundamental to barrier formation and cutaneous antimicrobial defense, and exogenous factors such as detergent, cosmetic products, occlusive dressings, and topical antibiotics could play a role in the pathogenesis of acne by influencing skin pH.20,21 Acne can therefore be considered a multifactorial disease,22–25 and although P. acnes is widely concluded to cause this disease and is thus the main target of most therapeutic protocols,26 defining a standard treatment regimen is still a great challenge to researchers.27 Currently, acne can be controlled with appropriate treatment,1 although improvements may take up to several months, and usually vanish when treatment is withdrawn. Furthermore, spontaneous improvement might also occur over time.

**Issues in the current management of acne**

As for other multifactorial diseases, a variety of different products, primarily pharmaceuticals, can be used to treat acne. Although topical preparations are most frequently used, systemic drugs are also indicated for severe acne.

Currently available systemic products include the retinoid isotretinoin, antibiotics, or oral contraceptives, all of which are indicated for more severe acne, acne resistant to other therapies, and nodulocystic, scarring acne. Although the mechanism of action of retinoids is still unclear,28 oral isotretinoin is considered the most effective medication available to date.27 Treatment with isotretinoin, however, is associated with the most serious side effects elicited by acne treatments, including exacerbation of acne, teratogenicity, and permanent side effects, a toll which is gradually restricting its regulation29,30 and use.31 Oral antibiotics are usually preferred for the treatment of acne located on the trunk, acne unresponsive to topical therapy, and in patients at a greater risk of scarring. Antibiotics effectively reduce the number of inflammatory lesions but do not completely clear the condition. Moreover, worldwide concern over the increasing resistance of P. acnes to erythromycin has prompted questions regarding the use of antibiotics for acne.32,33 Oral contraceptive preparations are combinations of estrogens and progestogens that work by suppressing sebaceous gland activity and decreasing androgen secretion. While hormonal therapies are considered an excellent choice for women who need oral contraception,34 it is not clear how they compare with alternative acne treatments.35

Topical preparations comprise retinoids and antibiotics, as well as many other active ingredients (mainly salicylic acid, azelaic acid, and benzoyl peroxide). Among topical preparations, combination products are increasingly popular, for example, retinoid and antibiotic, retinoid and zinc, retinoid and benzoyl peroxide, benzoyl peroxide and antibiotic, or benzoyl peroxide and antiseptic. Single-agent benzoyl peroxide preparations are, however, considered the gold standard for safety and efficacy in topical acne treatment.36 Benzoyl peroxide kills P. acnes by the generation and release of oxygen free radicals,37,38 while seborrhea remains unaffected (as for topical retinoids).39 Single-agent benzoyl peroxide preparations have demonstrated greater activity against inflammatory lesions than topical isotretinoin,40,41 and have proven as effective as a topical combination therapy of benzoyl peroxide and an antibiotic for people with mild-to-moderate facial acne.42 Further investigations are, however, required, since previous studies have suggested that some combinations with benzoyl peroxide (ie, with clindamycin43 or retinoic acid44) are superior to single-agent therapy. Unfortunately, benzoyl peroxide causes primary irritant dermatitis (erythema, dryness, desquamation, burning, and itching), and patients are advised to expect this side effect, and to discontinue therapy if it becomes severe.45 Low-percentage benzoyl peroxide...
preparations (2.5%–5%) are less irritating, and furthermore, there is no clear evidence that stronger preparations are more effective. 46 Other common topical agents include sulfur, resorcinol, sulfacetamide, aluminum, and zinc; however, data from peer-reviewed literature suggest that these agents have only limited efficacy. 47 Finally, current comparative evidence does not clearly support the use of topical dapsone 9 and taurine bromamine 48 for the treatment of acne.

Although acne is widespread with numerous treatment options available, 49 the condition is still not considered curable, prompting further investigation by the pharmaceutical industry. All mainstream products can cause severe side effects including, paradoxically, the typical signs and symptoms of acne, and there is therefore a demand for new innovative treatments.

Mode of action of Farmaka Acne Cream

The primary role of the skin’s acid mantle (pH 4.5–5.5) in barrier functionality, lipid synthesis, and in the direct and indirect regulation of microbiome is widely acknowledged 50–52 Alkaline cosmetics, detergents, 50–52 and also topical drugs including acne treatments 53 are thought to favor the onset or exacerbation of several different dermatological conditions, including acne. Farmaka Acne Cream (FAC) is a novel topical formulation developed to combat the signs of mild and moderate acne. FAC forms a layer of pH 4.0 on the skin, and thus creates a superficial acidic milieu, targeting both primary and secondary acne factors. Its principal effects include the following:

1. inhibition of P. acnes growth and metabolism;
2. restoration and maintenance of the skin’s acid mantle, barrier functionality, and moisture balance, thus contributing to the mitigation of acne signs and symptoms and potentially of the most common side effects of mainstream treatments.

FAC’s superficial film physically protects skin from dust, dirt, polluting elements, food residues, and sweat, the secondary factors that could trigger or exacerbate acne. 11 FAC is well tolerated, non-comedogenic, safe for ultraviolet exposure, perfume-free, and preservative- and paraben-free, and would appear to be a promising candidate for the adjuvant treatment of mild and moderate acne.

Notably, FAC’s film-forming ingredient is a polyol polymer. These chemicals are widely used in the pharmaceutical and cosmetic industry for their emollient and moisturizing properties. 54 They have also been thoroughly investigated as vehicles for the active principles in topical acne treatments, with reports of significant reductions in side effects such as irritation, dry skin, and desquamation but with no effect on overall efficacy. 55–61 FAC’s beneficial effect on the skin’s barrier functionality and moisture balance could also mitigate the main signs and symptoms of acne such as erythema, desquamation, burning, itching, dyschromia, and pain. As these manifestations of acne are also the most common side effects of the mainstream treatments, FAC could eventually complement their use, possibly reducing their adverse reactions and thus increasing patient compliance and overall therapeutic efficacy.

Preclinical efficacy of FAC

Acne severity and scarring have been linked to P. acnes inflammatory factors. 4,5 In particular, porphyrin concentration has been related to acne severity, 62 while enzymes such as phosphatases, proteinases, lipases, and hyaluronate lyase are known to participate in scarring. Like other bacteria, P. acnes growth and metabolism are highly pH dependent. Growth was reported to be greater in a pH range of 6.0–7.0 than in a more acidic milieu, 63 was promoted at pH values of 6.0 and 6.5, and was optimal at pH 6.7. 64 Moreover, maximum specific growth rates and optimum biomass production for P. acnes were both measured at pH 6.0. 65 Conversely, growth was inhibited at pH values of 5.0 and 5.5, 66 and no growth was observed at pH 4.0. 65 The secretion of metabolites, phosphatase, and proteinase was completely inhibited at pH 4.0, while the secretion of lipase and hyaluronate lyase was inhibited at pH 4.5. 63 Additionally, porphyrin concentration was reported to be three times higher at pH 6.1 than 5.3. 67

FAC has been formulated at pH 4.0 to enable optimal inhibition of P. acnes growth and metabolism. To investigate the beneficial effects of FAC, a proof-of-concept experiment was conducted in which the product was tested in vitro on cultures of P. acnes versus gold standard 5% benzoyl peroxide, the market leader brand. Both preparations caused a reduction of >3 log of the number of microorganisms after 6 hours of contact time (Table 1). 68 These data demonstrated that FAC is as effective as the active comparator in inhibiting or impeding bacterial growth. The inhibition of P. acnes growth and metabolism by FAC could be related to the creation of a superficial acidic milieu, as well as restoration of the skin’s acid mantle and commensal microbiome.

Efficacy and tolerability

As acne is always accompanied by erythema, desquamation, burning, itching, dyschromia, and pain, the efficacy and tolerability of FAC, an acidic product, were investigated clinically.
Initial testing was conducted in an open study of 32 subjects with mild or moderate acne on the face.24 FAC was applied to the face, and to the left and right side of the suprascapular region of the back. Subjects were examined prior to the first-product application, and after 4 weeks of twice-daily treatment. Efficacy was evaluated clinically in terms of the reduction of acne signs and symptoms (ie, erythema, scaling, number of open and closed comedones, papules, pustules, dyschromia, pain, burning, and itching). Additional assessments included follicular biopsy and morphometric analysis of sebum and photographic evaluation. Photographs were taken of the areas of acne in each subject prior to and at the end of treatment with FAC. For analysis of the comedolytic activity of FAC, follicular biopsies were performed in each subject. Samples of the cutaneous surface under investigation were taken by stripping an area of skin (5 cm × 5 cm) at baseline and at the end of the treatment period. The follicular biopsy was therefore a cast of the follicular infundibulum with associated hair and keratinic material. In acne skin or skin prone to acne, an increase in keratinic material can result in the formation of microcomedones, and eventually, clinically evident comedones. Statistical analyses of the density and total area of the comedones were performed using Student’s t-test or nonparametric tests. For analysis of sebum prior to and after treatment, Sebutape® (Cu-Derm Corp, Dallas, TX, USA) was applied to the skin for 60 minutes to enable the collection of sebum drops arising from the cutaneous surface. Computerized morphometric analysis of the sebum spots was used to determine the ratio of the surface covered by sebum and total surface area of the specimen and the mean dimensions of the sebum spots, that is, the area, diameter, and major and minor axes. Image analysis was performed on samples of the same area of the cutis using a stereomicroscope connected to an analogical video camera. Subjects were asked to judge the product’s efficacy, tolerability, and cosmetic acceptability.

Clinical data demonstrated that treatment with FAC reduced all of the major signs and symptoms of acne including itching, erythema, and scaling, with 38%, 86%, and 76% of subjects, respectively, showing significant improvement in these symptoms and none experiencing worsening. Additionally, reductions in the numbers of papules (~52%), pustules (~41%) (Figures 1 and 2), and open and closed comedones (~48% and ~45%, respectively) were observed. Overall, acne severity was clearly improved in 38% of the subjects, while none worsened. Furthermore, FAC was also found to be effective in controlling sebum secretion (Figures 3 and 4), and was non-comedogenic. Finally, 90% of subjects judged tolerability as good or very good, while clinical efficacy and cosmetic acceptability were both judged good. The authors reported an overall improvement of acne in 76% of subjects, and proposed that FAC should be considered a valid adjuvant for the treatment of acne.25 In a subsequent study, FAC was tested for contact sensitization and photosensitization, two common side effects of mainstream acne treatments, on 29 subjects affected by mild or moderate facial acne.60 FAC was applied to two symmetric

Table 1 Log reduction in growth of Propionibacterium acnes

| Contact time (hours) | FAC log reduction | BP 5% log reduction | Control log reduction |
|---------------------|------------------|---------------------|----------------------|
| 0                   | 0.06             | 0.04                | 0.06                 |
| 3                   | 2.59             | 2.83                | 0.02                 |
| 6                   | >3.87            | >3.87               | −0.02                |
| 12                  | >3.87            | >3.87               | 0.24                 |
| 24                  | >3.87            | >3.87               | 0.93                 |

Abbreviations: BP, 5% benzoyl peroxide; FAC, Farmaka Acne Cream.

Notes: (A) Before treatment. (B) After 4 weeks of treatment.
areas of each subject’s back daily for 10 days. One minimal erythema dose was delivered to one side of the back using a solar stimulator, beginning on day 11 and continued for the next 2 consecutive days (i.e., 3 days in total). Thus, four different subareas of treated/untreated and irradiated/nonirradiated and combinations thereof were created. Two skin areas were designated as controls: one area to which FAC was applied but not irradiated in order to determine whether contact sensitization could be linked exclusively to FAC, and another area irradiated for 3 consecutive days but without application of FAC. This second control area was intended to identify possible idiopathic reactions to solar irradiation. Clinical features of contact sensitization or photosensitization (erythema, itching, blistering, edema, and scaling) were assessed according to a three-point scale (0 = absent; 1 = mild; 2 = moderate; 3 = intense). No reports of contact sensitization or photosensitization were observed in the treated and nonirradiated areas. The author concluded that FAC should be considered safe for use in intense sunlight.

Conclusion

Despite being widespread with a large number of treatment options, acne is not considered curable. Moreover, mainstream treatments for acne can cause side effects, some of which are severe. FAC is an innovative film-forming cream with a synergetic mode of action that inhibits $P. \text{acnes}$ proliferation, restores the skin’s acid mantle and barrier functionality, and provides physical protection from acne secondary factors. In vitro and in vivo studies provide an initial body of evidence on the safety and clinical benefits of FAC, a promising candidate for the treatment of mild and moderate acne.

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