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ROSACEA
ACNE LIEVE O MEDIA
IAB, ten years in Dermatology

In November 2004, five Italian dermatologists (Vincenzo Bettoli, Daniel Innocenzi, Giuseppe Miceli, Giuseppe Monfrecola and Stefano Veraldi) founded in Milan, with the "blessing" of Stefano Calvieri and Ruggero Caputo, the Italian Acne Board (IAB). In January 2005, joined Mauro Barbareschi and Gabriella Fabbrocini. In February 2009, an absurd and tragic fate took away Daniele, who has been validly replaced by Nevena Skroza.

In May 2006, the Journal of Acne and Related Disorders came and its publication continued until the end of 2009, when the magazine changed its name (European Journal of Acne and Related Diseases) and publisher (Edizioni Scripta Manent). The first issue of the new journal was published in January 2010. The editorial board is international and it includes prestigious dermatologists such as Gerd Plewig (Monaco, Germany), Jacek Szpichtowski (Wroclaw, Poland), Robert Allen Schwartz (Newark, USA) and Shyam Verma (Ladodara, India).


In 2013 was also published “Acne”, the first book in English, edited by R.A. Schwartz and G. Miceli.

After the first editions organized in Rome by D. Innocenzi, Acne Day was organized by S. Veraldi (2009 to 2010 in Rome and Milan), by V. Bettoli (Ferrara 2011), by G. Monfrecola and G. Fabbrocini (2012 in Naples). The first "international" edition of Acne Day (Acne and Rosacea Days) was held in Milan in September 2013 and was organized by S. Veraldi and M. Barbareschi. The next Acne Day will be held in Naples in October 2014, and will be organized by G. Monfrecola and G. Fabbrocini. On the occasion of Expo 2015, the IAB is working for the organization of AcneRosaceaMilanExpo (the title is not yet final, however, as well as the date).

Some members of the IAB are part of important international boards: V. Bettoli is in the Global Alliance in Acne and in the European Alliance in Acne and S. Veraldi is in Rosacea Global Advisory Board and in the newborn European Board on Severe Acne (first meeting in Paris January 24, 2014).

Thank you all.

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²European Institute of Dermatology, Milan, Italy

Treatment of symptoms of erythematotelangiectatic rosacea with topical potassium azeloyl diglycinlate and hydroxypropyl chitosan: results of a sponsor-free, multicenter, open study

Summary

Thirty-seven adult Caucasian patients (9 males and 28 females), with erythematotelangiectatic rosacea accompanied by stingning and burning sensation, were treated with a cream containing 5% potassium azeloyl diglycinlate and 1% hydroxypropyl chitosan. All patients were previously treated at other centers with topical azeloyl acid and/or metronidazole. The cream was applied twice daily for 12 weeks. Objective of the study was the evaluation of the soothing effect of the cream: stingning and burning sensation were measured by means of a 4-point scale (0 = absent; 1 = mild; 2 = moderate and 3 = severe). All patients were clinically evaluated every 4 weeks. Thirty out of 37patients (81.1%) were considered evaluable. Before the beginning of the study, the total score of stingning and burning sensation was 66 (mean: 2.2 points/patient); at the end of the study, it was 37 points (<29) (mean: 1.2 points/patient), with a reduction of 56.1%. No side effects were reported or observed. This study shows that the fixed combination potassium azeloyl diglycinlate-hydroxypropyl chitosan is effective in reducing stingning and burning sensation in patients with erythematotelangiectatic rosacea.

Key words: Azelaic acid, glycine, hydroxypropyl chitosan, potassium azeloyl diglycinlate, rosacea.

Introduction

Rosacea is a common inflammatory disease of the central areas of the face that is characterized clinically by erythema, telangiectasias, papules, pustules and nodules. Furthermore, ocular involvement is not rare. The American National Rosacea Society Expert Committee classified the disease into four subtypes: erythematotelangiectatic, papulo-pustular, phymatous and ocular rosacea.¹,² Erythematotelangiectatic rosacea (subtype 1) is characterized by flushing, transitory and subsequently persistent erythema, and telangiectases. Comedones are absent. Stingning and burning sensation are very common and sometimes important symptoms.¹,²

We present the results of a sponsor-free, multicenter, open trial on the activity and tolerability of a cream containing a fixed combination of 5% potassium azeloyl diglycinlate and 1% hydroxypropyl chitosan in patients with erythematotelangiectatic rosacea accompanied by stingning and burning sensation.

Patients and methods

Thirty-seven Caucasian patients [9 males (24.3%) and 28 females (75.7%), with an age ranging from 28 to 71 years (median age: 46.7 years), with erythematotelangiectatic rosacea
accompanied by stinging and burning sensation, were treated with a cream containing a fixed combination of 5% potassium azeloyl diglycinate and 1% hydroxypropyl chitosan. All patients were previously, although unsuccessfully, treated at other centers with several topical products, including azelaic acid (19 patients), metronidazole (11 patients) or both (7 patients). The cream was applied, after a wash out period of at least two weeks, twice daily for 12 weeks. The application was preceded by a cleaning of the face. No other topical and/or systemic products or drugs were allowed, except for cleansers and sunscreens (all patients used the same cleansers and sunscreens). Moisturizers were not allowed. Objective of the study was the evaluation of the soothing effect of the cream: stinging and burning sensation were measured by means of a 4-point scale (0 = absent; 1 = mild; 2 = moderate and 3 = severe). All patients were clinically evaluated every 4 weeks.

Results

Thirty out of 37 patients (81.1%) were considered evaluable. Seven patients were lost during the trial and were therefore not considered as evaluable. Before the beginning of the study, the total score of stinging and burning sensation was 66 points (mean: 2.2 points/patient). After four weeks of treatment, the total score decreased to 59 points (-7; mean: 2 points/patient). Eight weeks later, the total score was 44 points (-22; mean: 1.5 points/patient).

At the end of the 12 weeks of treatment, the total score decreased to 37 points (-29; mean: 1.2 points/patient), with an improvement of 56.1%. The reduction of the total points from the beginning of the treatment to the end of the study was 29. The mean of the points/patient decreased from 2.2 to 1.2 points. No side effects were reported or observed.

Discussion

Potassium azeloyl diglycinate (or azelagic acid) is a new water soluble derivative of azelaic acid. It is obtained by reacting the chloride of azelaic acid with two molecules of glycine and one molecule of potassium hydroxide. Azelagic acid, like azelaic acid, has sebostatic and whitening action; furthermore, it possesses, thanks to the presence of glycine, a moisturizing effect.

Hydroxypropyl chitosan is a water soluble, semi-synthetic derivative of chitosan that, thanks to its adhesive properties, provides a protective film on the stratum corneum, with a barrier-like action. In vitro antimicrobial activities of hydroxypropyl chitosan and its derivatives were evaluated by the Kirby-Bauer disc diffusion method and the macro-tube dilution broth method. Hydroxypropyl chitosan and its derivatives exhibited no inhibitory effect on Escherichia coli and Staphylococcus aureus. However, an inhibitory effect was found against pathogenic fruit fungi (Alternaria mali, Coniella diploidiella, Fusarium oxysporum and Psylla piricola).

An experimental study showed that the fixed combination 5% potassium azeloyl diglycinate - 1% hydroxypropyl chitosan has an anti-inflammatory effect that is superimposable to that of 15% azelaic acid, although with a better tolerability.

Furthermore, a pilot, multicenter, randomized, double blind, placebo-controlled study confirmed the efficacy of this fixed combination in erythema and dryness in patients with subtypes I and II rosacea, using both the Mexameter® and Corneometer® devices.

As previously mentioned, the objective of our study was the soothing effect of this cream in patients with erythematotelangiectatic rosacea accompanied by stinging and burning sensation, that is, in patients with rosacea, as important as erythema and telangiectasia.

On the basis of the results of our study, we can state that the fixed combination potassium azeloyl diglycinate-hydroxypropyl chitosan is effective in reducing stinging and burning sensation in patients with erythematotelangiectatic rosacea. However, this action is slow: in fact, only very mild improvement of symptoms was recorded after four weeks of treatment.

It is possible that this action is due to both hydro-
ypropyl chitosan that, as previously stated, improves the skin barrier function of defense against environmental physical and chemical insults, and glycine, that provides a moisturizing effect and enhances the stratum corneum hydration. A controlled clinical trial is necessary in order to confirm these results.

 Declaration of interest:
The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.

References
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Nipacide: a new way as topical antiseptic in acne

**Summary**

Nipacide at higher concentrations can kill both bacteria and skin cells by breaking down their membranes. At lower concentrations, it kills bacteria by shutting down their ability to use fatty acids. Since acne bacteria feed on fatty acids, nipacide causes them to starve. The issue with using products that contain nipacide, such as body clearing lotion, is that using it at high concentrations damages the skin, and using it at low concentrations kills Propionibacterium acetn. In cytotoxic tests nipacide showed cytotoxic effect at higher concentrations, vice versa showed non irritant action in the preclinical rabbit tests. Nipacide 4.8% w/v: a chemical compound with the formula C₈H₁₄ClO and CAS number 88-04-0. It is commonly used in antibacterial soaps; in agar patch studies, it has been found to kill a wide variety of microbes, including bacteria, fungi, and the superbug MRSA, within 15 seconds. Its antibacterial action is due to disruption of cell membrane potentials, blocking production of adenosine triphosphate (effectively starving the cells). Nipacide showed in agar tests that 5000 ppm (0.5% concentration) is far above the effective antimicrobial level. Nipacide has a broad spectrum of activity which includes the following common spoilage organisms: nipacide PX chloroxylenol provides a broad spectrum of antimicrobial activity. Nipacide PX is effective against both Gram-positive and Gram-negative bacteria, yeasts and fungal microorganisms. In the pivotal clinical studies nipacide-sA or zinc oxide cream showed that it is as effective as BP gel in the treatment of papulo-pustular and comedonal acne and that it is better tolerated. In conclusion, this approach to the treatment of acne can be useful in the dermatologist therapeutic tools.

**Key words:** Acne, biocide, chloroxylenol, nipacide (chloroxylenol with high degree of purity), parachlorometaxenol.

**Introduction**

Chloroxylenol, also known as parachlorometaxenol (PCMX) or nipacide, the pharmaceutical grade of chloroxylenol (purity 99.3%), is an antimicrobial agent used to control the growth of bacteria and fungi. It is also used to disinfect a variety of surfaces (diapers, laundry equipment, bathrooms, laundries). Chloroxylenol was recorded in the United States in 1959 as a fungicide. It is a halogen-substituted xylene that acts by means of cell wall disruption and enzyme inactivation. Nipacide is used as active ingredient in over-the-counter products or drugs and as preservative for cosmetics and personal care products currently on the market.

**Material and methods**

We performed a careful review of the literature on the role of biocides in acne by means of Cochrane Library, Food and Drug Administration and Medline database. In particular, we reviewed chloroxylenol and PCMX.

**Results**

**Laboratory tests**

Chloroxylenol is less active than chlorhexidine gluconate (CHG). However, it has a good activity against Gram-positive and Gram-negative bacteria. It is especially active against...
Pseudomonas sp. Furthermore, its activity is potentiated by the addition of ethylenediaminetetraacetic (EDTA). On the other hand, PCMX has a low activity against Mycobacterium tuberculosis and fungi \(^1\). PCMX has been shown to be less effective than either CHG and iodophors in reducing skin flora. An expert panel of toxicologists stated that PCMX, when applied on the skin, is safe at concentrations up to 4.8% \(^2\). The incidence of skin sensitization by PCMX is low. Rapidity of activity of PCMX is intermediate and it has a persistent effect for a few hours. It is active at alkaline pH, but it is neutralized by non-ionic surfactants. For this reason, the efficacy of PCMX, like CHG, is highly formula-dependent. PCMX is currently available in a number of hand-washing products, usually at concentrations ranging from 0.5 to 3.75%.

Nipamide provides a broad spectrum of antimicrobial activity. It is effective against both Gram-positive and Gram-negative bacteria, fungi and yeasts. The minimum inhibitory concentrations (MIC) of nipamide are listed in Table 1 \(^3\).

Chloroxylenol has low to moderate oral, dermal and inhalation acute toxicity. In an acute oral toxicity study with rats, the LD was 3.83 g/kg.

In another acute oral toxicity study with rats, the LD was higher than 5 g/kg. An acute dermal toxicity study in rats resulted in an LD higher than 2.0 g/kg. An acute inhalation toxicity study in rats showed an LC higher than 6.29 mg/l.

Chloroxylenol was toxic in acute irritation studies. An eye irritation study in rabbits found mild to severe corneal opacity in unwashed eyes, with irri-

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Nipamide PX Chloroxylenol MIC</th>
<th>Microorganisms</th>
<th>Nipamide PX Chloroxylenol MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus faecalis (^7)</td>
<td>20-167</td>
<td>Aspergillus niger (^4)</td>
<td>20-200</td>
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<td>Staphylococcus aureus (^5)</td>
<td>10-167</td>
<td>Penicillium funiculosum</td>
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<tr>
<td>Salmonella typhi (^2)</td>
<td>20-60</td>
<td>Trichophyton mentagrophytes (^3)</td>
<td>20-1,000</td>
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<tr>
<td>Escherichia coli (^8)</td>
<td>40-250</td>
<td>Penicillium citrinum</td>
<td>250</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (^9)</td>
<td>80-1,000</td>
<td>Penicillium luteum</td>
<td>125</td>
</tr>
<tr>
<td>Bacillus subtilis (^2)</td>
<td>50</td>
<td>Penicillium chrysogenum</td>
<td>1,000</td>
</tr>
<tr>
<td>Citrobacter sp. (^2)</td>
<td>167-250</td>
<td>Alternaria solani</td>
<td>200</td>
</tr>
<tr>
<td>Corynebacterium pyogenes</td>
<td>60</td>
<td>Trichophyton rubrum</td>
<td>60</td>
</tr>
<tr>
<td>Enterobacter aerogenes (^4)</td>
<td>30-156</td>
<td>Trichophyton tonsurans</td>
<td>250</td>
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<tr>
<td>Klebsiella pneumoniae (^5)</td>
<td>167-250</td>
<td>Epidermophyton floccosum</td>
<td>30</td>
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<tr>
<td>Mycobacterium avium</td>
<td>125</td>
<td>Saccharomyces bayanus</td>
<td>50</td>
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<td>Proteus mirabilis (^7)</td>
<td>125-467</td>
<td>Candida albicans (^2)</td>
<td>50-125</td>
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<td>Salmonella choleraesuis</td>
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<td>Mucor racemosus</td>
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<td>Micrococcus luteus</td>
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<td>Mycobacterium smegmatis</td>
<td>167</td>
<td>Torula ramosa</td>
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<tr>
<td>Proteus vulgaris (^2)</td>
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<tr>
<td>Acinetobacter calcoaceticus</td>
<td>83</td>
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<tr>
<td>Bacillus cereus</td>
<td>50</td>
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<td></td>
</tr>
<tr>
<td>Serratia marcescens (^5)</td>
<td>20-167</td>
<td></td>
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<tr>
<td>Pseudomonas cepacia</td>
<td>40</td>
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<td></td>
</tr>
<tr>
<td>Enterobacter gergoviae</td>
<td>250</td>
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tation that persisted for 14 days. Eyes washed four seconds later developed mild to moderate erythema, edema and discharge, without corneal damage: all of them decreased within five days. Another rabbit eye study, with a 30% solution, found marked corneal opacity that did not improved within 72 hours. A third rabbit eye study concluded that chloroxylenol was corrosive.

Chloroxylenol is not a dermal irritant or sensitizer. A dermal irritation study with rabbits showed mild irritation lasting less than 48 hours. Chloroxylenol did not produce dermal sensitization in guinea pigs. A repeated insult patch test in humans showed no skin sensitization or irritation. A sub-chronic dermal study was carried out in albino rabbits. Some animals were treated for 21 days and others for 90 days. The dose levels were 180 mg/kg/day of chloroxylenol.

The systemic No-Observable-Effect-Levels (NOEL) was 180 mg/kg/day and the NOEL for skin irritation was 18 mg/kg/day.

The Lowest Observable Effect Level (LOEL) for skin effects was 180 mg/kg/day, where erythema, coriaceous areas, and fissuring were found.

A toxicity study was carried out in Sprague Dawley rats with dose levels of 0, 100, 500, or 1.000 mg/kg given by gavage (gastric tube) on gestation days 6-15. The maternal NOEL was 100 mg/kg/ day. The maternal LOEL was 500 mg/kg/day, based on decreased weight gain and food consumption. There were deaths at the high dose. The NOEL for developmental toxicity was 1.000 mg/kg/day. An Ames mutagenicity study in Salmonella typhimurium concluded that chloroxylenol was negative in inducing reversion in the standard strains, with and without activation. In a test of unscheduled DNA synthesis in primary rat hepatocytes, the chemical did not induce a genotoxic effect up to cytotoxic levels. No evidence of mutagenicity or genetic toxicity was found in an in vivo mouse micronucleus assay.

Metabolic tests with 25% chloroxylenol solution in Sprague Dawley rats demonstrated that this product is eliminated in the first 24 hours, mostly in the urine, with small amounts in the feces, after oral or dermal exposure.
Following dermal exposure, about half of the product was not absorbed. High concentrations were found in the kidney, which indicates excretion in urine. Concentrations in the lungs indicates some elimination in expired air. In another study, beagle dogs dosed orally excreted virtually all of the chloroxylenol in the urine within 24 hours. A small amount was present in the feces, but essentially none remained in any tissue. The chemical was excreted in conjugated form with little free chloroxylenol. Chloroxylenol is widely used in the prevention of infections of the skin and for the disinfection of objects and equipment, as well as environmental surfaces. The antimicrobial properties of chloroxylenol and other chlorinated phenols have been extensively studied. The antimicrobial properties of the disinfectant to certain pathogenic bacteria have been widely reported (Figure 1).

**Clinical tests**

Below is a review of available data on the clinical use of chloroxylenol and chloroxylenol with salicylic acid (SA). These figures also include observational experiences that have evaluated the efficacy and safety of product formulated cream. In a clinical study, 51 subjects completed a controlled, randomized, double-blind trial comparing the following compounds: one group was treated with a cream containing chloroxylenol and zinc oxide (Nels); a second group with 5% benzoyl peroxide (BP) cream, and a third group with the vehicle of the cream Nels. Drugs were applied twice a day for 8 weeks. At the end of the study there was no significant difference in counts of non-inflammatory and inflammatory lesions and in the reduction of the inflammatory component in the groups of patients treated with the cream Nels and BP. Both creams have proved superior to the vehicle. The assessment of effectiveness on the part of subjects and investigators showed no significant differences between Nels cream and BP. However, the side effects, such as flaking and dryness were significantly lower in the group of patients treated with the cream Nels. Furthermore, a 12 weeks randomized, double-blind study was carried out to compare 5% BP gel and 0.5% chloroxylenol and 2% Salicylic Acid (PCMX+SA) cream (Nisal cream), to evaluate the efficacy and tolerability of both products. Thirty-seven volunteers were enrolled, 19 in the BP group and 18 in the group PCMX+SA. The patients applied the medication twice daily on the face. The clinical evaluation of the lesion count were evaluated at 0, 3, 6, 9 and 12 weeks. At week 12, the two groups showed a significant improvement in both inflammatory and non-inflammatory lesions (60% and 54% for the BP group, and 62% and 56% for the PCMX+SA group, respectively). Although PCMX+SA showed a slightly better keratolytic effect for the entire period of the study, there was no statistically significant difference in the reduction of papules, pustules and comedones between the two groups. Side effects, such as erythema and photosensitivity, were significantly less severe in PCMX+SA group at week 12 (p = 0.0002 and p = 0.05, respectively). These results suggest that PCMX+SA is effective as BP in the treatment of comedonal and papular acne, but is better tolerated. The therapeutic effects of this treatment were at the beginning considered to be most likely due to the antibacterial activity of chloroxylenol against *P. acnes*. However, there was no bacterial involvement in this experimental model. It was therefore speculated that the inhibitory effect of PCMX+SA is probably due to a mechanism other than its antibacterial activity. Although macroglol, which is used as the ointment base, has high affinity and compatibility with free fatty acids such as oleic acid, it is a water-soluble substance, and thus inhibits transdermal absorption of any substances dissolved in it. Therefore, it was suggested that macroglol may have inhibited comedone formation by dissolving and removing free fatty acids, such as oleic acid, thereby preventing them from stimulating the follicular endothelium, leading to suppression of abnormal keratinization.

**Discussion**

New therapies for the treatment of acne include biocides, in several formulations.
The introduction in the market of novel biocide formulations can induce many advantages. These biocides are effective against a variety of Gram-positive and Gram-negative bacteria, effective and well tolerated. This biocide may be used as monotherapy or in combination therapy. In fact, it can be is used with SA to increase the activity against acne, increasing the synergistic effect of these agents. Side effects of this biocide are much less common and severe compared with other topical anti-acne drugs and products. With regard to the need to prevent antibiotic resistance, non-antibiotic substances with anti-inflammatory and anti-bacterial effect would provide a potential benefit. The existing experimental and human studies of phytotherapeutics in acne therapy were recently reviewed. Various natural substances and biocides showed anti-inflammatory effect in in vitro or animal studies and some substances were successfully tested in humans.

**Conclusions**

In conclusion, chloroxylenol ointment has inhibitory effects on the formation of comedones and can be used for the treatment of existing comedones. Therefore, it is a useful topical medicine for the treatment of early-stage acne and for preventing acne. We consider that further work will be necessary to obtain a better understanding of the actions of this product, studying more deeply to analyze the key mechanisms by which it inhibits acne lesions formation.

**References**

A case of acneiform eruption likely due to lamotrigine

**Summary**

Drug-induced acne typically presents with monomorphic lesions subsequent to the administration of a medicine, unusual distribution of manifestations beyond seborrheic areas, resistance to conventional therapy and response to withdrawal of the causative agent. Here we present the case of an acneiform eruption likely associated with epilepsy treatment with lamotrigine in a 35-year-old woman without previous history of acne vulgaris during teenage.

**Key words:** Drug-induced acne, acne vulgaris, lamotrigine, acneiform eruption.

**Introduction**

Lamotrigine [3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine] is a phenyltriazine derivative used for the treatment of epilepsy and bipolar disorder. The dose regimen starts from 50 mg/day and may be increased with a slow titration schedule to a maximum of 500 mg/day divided in two doses. Its mechanism of action is supposed to be suppression of rapid sustained neuronal firing and inactivation of Na+ channels. Lamotrigine is completely absorbed from the gastrointestinal tract after oral administration, and is metabolized by glucuronidation.

Side effects usually consist of dizziness, headache, blurred or double vision, nausea, vomiting, ataxia and drowsiness. Immuno-mediated maculopapular, urticarial or morbilliform skin rashes and few cases of Stevens-Johnson syndrome have also been described.

To our knowledge, only two other cases of acneiform eruptions associated with lamotrigine have been reported so far. We present the case of a young woman without previous history of acne vulgaris, who was affected by an extensive acneiform eruption after treatment with lamotrigine.

**Case report**

A 35-year-old Caucasian woman, without previous history of acne vulgaris, was admitted to our department because of sudden onset of papules, pustules and comedones on her face and upper trunk. She was affected by Type 1 diabetes mellitus under treatment with insulin since she was ten years old, and by borderline personality disorder under treatment with fluoxetine since five years. One year before the admission, she had suffered from epileptic seizures associated with marked hyperglycemia, therefore the neurologist
prescribed lamotrigine 50 mg bid as prophylaxis. She reported the sudden outbreak of a skin eruption associated with pruritus after six months of treatment, simultaneously with the beginning of solar exposure on summer and the increase of the dosage to 50 mg + 75 mg/day. The neurologist refused discontinuation of therapy, and after further six months of therapy the patient came to our observation.

At dermatological examination, she presented with diffuse scattered comedones especially on the face (Figure 1); inflammatory papules and pustules on the upper chest, trunk, shoulders and neck (Figure 2 and 3); and excoriated papules on the posterior scalp (Figure 4), where she reported scratching. General physical examination, pelvic ultrasound and serum androgen levels were normal. She was given for the first time a specific treatment with the topical combination of clindamycin and benzoyl peroxide. After one month of follow-up, the eruption showed good response with partial remission of the clinical picture, despite continuation of therapy with lamotrigine.

Discussion

There are no specific criteria to define drug-induced acne, but the potential relationship between drug ingestion and acne may be supported by several characteristics.

This case presents with the following clues: temporal relationship (also in the two other cases of acne potentially due to lamotrigine described in literature the eruption appeared after several months of treatment); unusual age of onset, that is after teenage (> 30 years); sudden outbreak of the eruption without previous history of acne vulgaris.

We did not find any published case of acneiform eruption associated with insulin nor fluoxetine. Nonetheless, this case lacks some other possible features suggesting the aetiologic role of a drug in acneiform eruption: it was not resistant to conventional acne therapy; the eruption did not extend beyond seborrheic areas. Moreover, the manifestations were not all in the same stage, as we have seen both retentional and inflammatory lesions, even though comedones were concentrated on the face, and papule-pustules on the upper trunk.

The patient was admitted several months after the beginning of the eruption, and we do not have any description of the clinical picture at early stages. Jeremy, et al. have suggested that mild inflammation may play a role as initial trigger of acne lesions in acne-prone skin, contesting the classical hypothesis that micro-comedones represent the very beginning of acne, and corticosteroids-
related acne is characterized by an initial phase of inflammatory lesions, which are succeeded by comedones. Therefore, the absence of a monomorphic clinical pattern in this case may not be considered sufficient to exclude the pathogenetic role of lamotrigine, even though its mechanism of action is unclear and sun exposure implication, as reported by the patient, is uncertain. Finally, we can not further support the relationship by means of a possible response to lamotrigine withdrawal nor rechallenge, since the neurologist did not agree with suspension nor substitution of the drug. According to our point of view, there is still high suspicion of lamotrigine role in inducing the clinical picture, and this case further stresses the importance of an accurate pharmacological history in every adult patient with acneiform lesions.

References

Acne keloidalis nuchae

Summary

Acne keloidalis nuchae is a chronic inflammatory process involving the hair follicles of the occipital scalp, occurring preferentially in young men of African descent. The etiology is unknown, but thought to be related to an ingrown process initiating by hair cut. However, association with acanthosis nigricans, a skin marker of metabolic syndrome has been recently reported. Clinically, the disease evolve in 3 clinical stages characterized by inflammatory papulo-pustular lesions going towards scarring and firm papules which coalesce progressively to form a large keloid-like fibro-cicatricial plaque. Therapeutic strategy is based on stage of the disease.

Key words: Acne keloid, folliculitis, nape of the neck, African ancestry.

Introduction

Acne keloidalis nuchae (AKN) is a chronic inflammatory process involving the hair follicles of the nape of the neck and the occipital scalp, occurring preferentially in young men of African descendant and typically characterized by papulo-pustular lesions ending to keloidal papules or plaques. This condition of unknown etiology is a common reason for medical consulting among Black patients. Unlike its height frequency, there are few publications about AKN in medical literature. Although it is not a life-threatening disease, AKN is a cosmetically disfiguring disorder which has a significant impact on the quality of life. The difficulty of its treatment justifies the multiplicity of therapeutic modalities.

Historic

AKN was first diagnosed by Ferdinand Ritter von Hebra in 1860 as «raspberry like syco-

sis». Later in 1869, Moritz Kaposi described it as Dermatitis papillaris capillitis. Ernest Bazin originated the term acne keloidal in 1872 which is still used. Although AKN is a pilo-sebaceous unit’s disorder, the term AKN is a double misnomer in that: it is neither a variant of acne vulgaris, as there are no comedones and cysts, nor a keloid as the exci-
sion does not always end to a recurrence. Then fibrosing folliculitis of the nuchae seems more appropriate.

Epidemiology

The prevalence ok AKN among general population is unknown. But it consists between 0.45% and 3.7% of all skin diseases affecting African population. Its represent about 2.8% of medical visits in Africa with some variations in different regions (9.4% in Nigeria, 3.5% in Cape
Town (South Africa), and 0.7% in Cotonou (Benin)\(^5,6\).
A higher frequency (13.7%) was recorded among Afro-Caribbeans attending a London skin clinic\(^7\).  
AKN particularly affects young people. It occurs usually between the ages of 16-35 years with mean onset age of 29 years\(^8\). Occurrence before puberty or after the age of 50 is very rare.  
AKN occurs almost exclusively in men of African descendant. However, it has occasionally been reported in Hispanics, Asians and rarely in Caucasians males and Black females (sex ratio 20:1)\(^9,10\).

Pathogenesis

The pathogenesis remains unclear and various theories have been proposed although none are conclusive. The primum movens seems to be follicular, but remains undefined. The pathogenic process is likely more similar to pseudofolliculitis barbae (PFB) than to acne vulgaris or to keloid formation. Indeed, the predilection of AKN for Africans is thought, by many authors, to be related to the particular conformation of the curved shape with elliptical section and oblique growth of African hair, which makes it to have a tendency to ingrown after cutting. The repeated shaving which outcomes a cropped hair style and frictions are initiating or worsening factors. The lesions start in 90% of patients after a haircut. It is also showed that the disease prevalence is highest after hair cut by razors (10.7%), followed by clippers (5.9%) and depilatory creams (0%)\(^5\). Africans tend to shave closely, by application of the metal of the clipper directly to the scalp or achieving the clean-shave by razor blade for sharpening the hair line.  
This process is often accompanied by symptoms (papules, crusts). This close shaving leads the cut end of the hair sharply pointed which either pierces the hair follicle wall during its growth (trans-follicular penetration) or growing in curved way leading to its re-entry into the skin (extra follicular penetration) (Figure 1).  
This process provokes a secondary inflammatory response around the hair follicle and subsequent development of fibrosis as in PFB.  
The destruction of the hair follicle results in a further “foreign hairs” granulomatous inflammatory reaction, leading in turn to fibrosis which clinically manifests as keloid-like scars and plaques\(^11,12\).  
In our experience, it is not uncommon to find pseudofolliculitis capitis’s lesions on the vertex besides of AKN ones. Association with PFB is also possible\(^4\).  
In addition to this concept of ingrown-hair, others proposed theories for which there is limited evidence are suggested.  
These factors that acting at puberty include:  
- Constant irritation of the posterior aspect of the neck by shirt collars or wearing a helmet\(^13\). This concept raised especially in Caucasians, does not seem to play a significant role in our experience.  
- Secondary AKN due to certain drugs (as ciclosporin, carbamazépin, hydantoin) has been also reported in Caucasians.  
- A genetic factor seems to be\(^14\) involved, but the condition is not especially associated with a family history of AKN nor a personal tendency of keloid formation. Furthermore, recurrences are uncommon after entire excision.  
- The role of autoimmunity has also been discussed.  
- Finally AKN is also speculated to be a primary form of scarring alopecia.

**Figure 1.**

The ingrown process.

Extrafollicular penetration.

Transfollicular penetration.
Figure 2. Acne keloidalis nuchae: inflammatory stage with papulo-pustular lesions.

Figure 3. Acne keloidalis nuchae: stage of fibro-cicatrical papulo-nodules.

Figure 4. Acne keloidalis nuchae: Stage of keloidal tumor.

Figure 5. Acne keloidalis nuchae associated with pseudofolliculite capitis and pseudofolliculitis barbae.

Figure 6. Differential Diagnosis of AKN: Darrier-Ferrand dermatofibrosarcoma of the nuchae.
No association with internal disease has been described so far, except with acanthosis nigricans, a skin marker for the metabolic syndrome. The reason for disease predominance in males is not clear, but it may partly result from differences in hairstyles between men and women but not hormonal influence. Likewise, the anatomic location of the lesions on the posterior aspect of the neck and occipital region is still undetermined.

**Clinical Presentation**

The mean duration of symptoms before consultation varies often between 12-29 months. Lesions usually start as a folliculitis with inflammatory follicular papulopustulosis (Figure 2). These lesions evolve towards small, scarring, firm, keloid-like and skin-coloured papulo-nodules, centered sometimes by several hair shafts (polytrichia) (Figure 3). The individual papules coalesce progressively to form larger fibro-cicatricial plaque of keloid-like aspect which can measure more than 5 cm of width (Figure 4). The disorder occurs constantly on the nape of the neck and occipital area. Sometimes, it realizes a central plaque of alopecia surrounded by an active papulo-pustular border. The lesions are often asymptomatic, but pruritus can be present. The course is generally progressive and chronic, but lesion size does not appear to be in relation with the disease duration. In our experience, we note a frequent association with a chronic peri-folliculitis of the vertex which is induced by shavings (psuedofolliculitis capitis) (Figure 5). In practice, for therapeutic regard, the evolution of the disease is classified in 3 clinical stages often entangled:

- Inflammatory stage with papulo-pustular lesions.
- Stage of scarring papules.
- Stage of keloidal tumor.

**Bacteriology**

Cultures are invariably negative as these abscesses are sterile. In the rare case of bacterial growth, it is probably a secondary infection by previous rupture.

**Histopathology**

The diagnosis of AKN is clinical. Early lesions of AKN show a dense peri-follicular infiltrate most intense at the level of the isthmus and lower infundibulum. It is composed of a mixture of lymphocytes, plasma cells, neutrophiles and histiocytes. Advanced lesions show a foreign body granulomatous reaction surrounding broken hair fragments.

**Differential diagnosis**

Post traumatic keloids of the nuchae and dermatophytic mycetoma can be confounded with AKN. In rare case, Darrier-Ferrand dermatofibrosarcoma can be located at the occipital scalp and leads also to a differential diagnosis (Figure 6). AKN should not be confounded either with the Quinquaud decalvans folliculitis which seems to be a subset of acne and sometimes is associated with acne conglobata and/or hidradenitis suppurativa.

**Treatment**

Starting treatment as early as possible gives the best results and can stop the disease process. The treatment strategy is based on stage of the disease.

*Inflammatory stage is generally managed by antibiotics*

It is based on oral or topical antibiotics for long period. Cyclines with a dose of 100-200 mg per day because of their antimicrobial and anti inflammatory effect are the first-line treatment. Minocycline should be avoided because of its fre-
quent induction of DRESS in Black population. Different topical antibiotics eg erythromycin, rifampin, clindamycin, quinolones are recommended by some authors when the number of lesions is limited. Oral zinc may be also effective. Systemic and topical retinoids are always ineffective. The addition of potent topical steroid can be particularly benefic. Normally, laser hair removal in inflammatory stage can also stop the disease process, resulting in an improvement.

In fibrotic papules stage, 3 options exist which can be used in association or by alternation

Series of intralosomal injections of steroids by a monthly interval for 3-6 months is effective. They should be done with a fine needle or Dermojet®, precisely into (and not under) the fibrotic papules. In addition, these injections are following by applications of potent or super-potent topical corticosteroid which alone are not effective. General corticotherapy is of no benefit and should be avoided. Cryotherapy can be benefic but in our experience, can cause a sequellar hypopigmentaion and scarring alopecia. Lesional punch excision of individupal papule followed by second intention healing is an alternative treatment. Electrocoagulation should never be used. Laser-assisted hair removal (using carbon dioxide or Nd:YAG) has been tried with some success in inflammatory and keloidal papules.

Tumoral stage

Once keloid has developed, the medical treatment is useless and a surgical intervention is often required. Intrallesional infiltration and cryotherapy are often ineffective. Excision of the involved area is the most effective treatment. Best results are achieved when the excision has a horizontal ellipse including the posterior hairline and reaches the deep subcutaneous tissue (removing therefore the follicular unit).

A second-intention healing of the postoperative site gives cosmetically acceptable results. For prevention of new lesions, the adjacent skin must not be shaved before excision. The patient should be also treated with immediate postoperative intrallesional steroid to the surgical site.

Prevention

Education is the key of prevention. It is based on the avoidance of friction and short haircuts, especially along the posterior hairline. The use of razors should be definitively forbidden. The shaving can be temporarily discontinued. It can be done later by using clipper and respecting the hair direction.

Conclusion

AKN is a chronic inflammatory process mostly seen in African descendant, principally the young men. Although it is aesthetically a distressing disease, early treatment reduces its disfiguring effects. The predilection for the nape of the neck, the triggering factors and the possible associated internal conditions are not still fully understood.

References


Rosacea: what’s new?

Introduction

Rosacea is a common and chronic disorder, characterized by flushing and persistent erythema in the central facial area. This disease has considerable psychosocial impact and causes embarrassment, anxiety and low self-esteem. It affects approximately 10% of the general population. Most individuals are of Northern European origin and up to 1/3 have a family history of the disorder. Recently, rosacea has been considered as an inflammatory disorder in the context of an altered innate immune response.

It has been proposed that environmental changes, which may include UV light exposure, hormone balances, and microbe challenges (by pathogens such as *Demodex folliculorum*), are sensed by pattern recognition receptors of the immune system. Subsequent signaling-induced effector molecules such as reactive oxygen species (ROS), cytokines, cathelicidin and chemokines may then modify dermal structure through vascular changes, collagen degeneration, lymphohistiocytic infiltration and neutrophil recruitment, which may perpetuate this response. Given this model, it is clear why most current therapies attempt to modulate various points of this inflammatory cascade (Figure 1).

Concerning etiology, *Demodex folliculorum* has been considered as the main etiologic factor of rosacea. New studies have showed that antigenic proteins of *Bacillus oleronius* (nonmotile gram-negative *Demodex*-associated bacteria) stimulate the abnormal inflammatory response of rosacea. Innate immune mediators, induced by *Bacillus oleronius*, have not been measured in patients with rosacea; however, neutrophils isolated from healthy volunteers and exposed to *Bacillus oleronius* proteins exhibited increased migration and production of matrix metalloproteinase-9, interleukin-8, and tumor necrosis factor. Correlation of *Helicobacter pylori* infection and rosacea is controversial and inconsistent among clinical observations. Several reports showed seropositivity to *H. pylori* in rosacea individuals. Eradication therapy for gastric *H. pylori* infection showed preferable outcome for rosacea symptoms thought it is not clear if the improvement of rosacea is due to *H. pylori* eradication. *H. pylori* produces ROS and rosacea individuals showed higher ROS including nitric oxide (NO) in plasma than controls.

A new pathogenic mechanism has been recently
suggested after a relationship was observed in a study where 46% of prospective patients with rosacea had small intestinal bacterial overgrowth (SIBO). After therapy with rifaximin, a nonabsorbed, gut-active antibiotic, complete resolution of cutaneous lesions in 78% of the patients with SIBO was observed.

Finally, it is likely that the increase in vascularity and in the temperature of the skin, in rosacea, may represent an important step in stimulating the usually commensal organism *Staphylococcus epidermidis* to behave as a pathogenic organism, leading to the development of papulopustular rosacea.

Cathelicidin and serine protease activity is also clearly involved in the pathogenesis of rosacea. It has been demonstrated that elevated epidermal serine protease activity occurs in rosacea and causes the deposition of cathelicidin-derived peptides in the skin. These peptides have the ability to cause inflammation when injected in the skin. Interestingly, it has been demonstrated that Toll-like receptor (TLR)-2 expression is altered in rosacea skin, which enhances skin susceptibility to innate immune stimuli and leads to increased cathelicidin and kallikrein production (Figure 1).

**Treatment of rosacea**

Although several medications are approved for the treatment of inflammatory lesions of rosacea, there is currently no approved medication directly targeting erythema of rosacea. While the exact cause of erythema of rosacea is not known, it is hypothesized that erythema results from the dysregulation in the cutaneous vasomotor responses, which leads to abnormal dilatation of facial blood vessels upon various stimuli. In USA, brimonidine tartrate is actually available as a 0.33% gel, it is a highly selective α2-adrenergic receptor agonist with vasoconstrictive activity. It has been approved by FDA for topical treatment of adults with persistent facial erythema of rosacea. This drug should be applied once daily to each of 5 areas of the face (central forehead, chin, nose, and each cheek). It is generally well tolerated; in rare cases flushing, skin burning sensation and contact dermatitis are reported. Recently, gene expression and protease activity were measured in laboratory models and patients with rosacea during a 16-week multicenter, prospective, open-label study of 15% azelaic acid (AzA) gel. AzA directly inhibited KLK5 in cultured keratinocytes and gene expression of KLK5, *Toll-like receptor-2*, and cathelicidin in mouse skin. Patients with rosacea showed reduction in cathelicidin and KLK5 messenger RNA after treatment with AzA gel. Subjects without rosacea had lower serine protease activity (SPA) than patients with rosacea. Distinct subsets of patients with rosacea who had high and low baseline SPA were identified, and patients with high baseline exhibited a statistically significant reduction of SPA with 15% AzA gel treatment. On the basis of these findings, it is possible to suggest a new mechanism of action for AzA and that SPA may be a useful biomarker for disease activity.

Concerning systemic therapies, isotretinoin has been reported to be effective for treating rosacea, including rhinophyma with a reduction in size and number of sebaceous glands. This drug can be used in resistant and recidivant rosacea with doses ranging from 0.5 to 1 mg/kg/day. It may be an alternative therapy, especially in men and in women beyond childbearing. Although this treatment does not cause antibiotic resistance, vigilance is required because of adverse side effects.

Continuous microdose isotretinoin may be applicable in selected cases to control flares as recently demonstrated by Park. Therapy with oral isotretinoin (< 0.5mg/kg/day) for per 3-4 months, in association with systemic steroids (prednisone 1 mg/kg/day for 1-2 weeks), has been useful in cases of rosacea fulminans, also known as pyoderma faciale.

In 2006, the anti-inflammatory dose doxycycline (ADD) 40 mg extended-release capsule once daily has been approved by the United States Food and Drug Administration (FDA) for treatment of rosacea. This subantimicrobial dosage is active on papulopustular lesions with rapid action (six weeks), favorable safety profile and absence of antibiotic selection pressure. The new 40 mg doxycycline is composed by 30 mg immediate-release and 10 mg delayed-release beads.
A much lower incidence of gastrointestinal side effects has been noted with ADD once daily compared to doxycycline 100 mg once daily \textsuperscript{18}. Patients with ocular involvement may benefit from subantimicrobial doxycycline too. Therapy with subantimicrobial dosing of doxycycline can modulate the inflammation of rosacea, by inhibition of chemotaxis and granuloma formation, inhibition of proinflammatory cytokines, NO and ROS without exerting antibiotic pressure responsible for the emergence of antibiotic resistance. The combination therapy approach of anti-inflammatory dose doxycycline and metronidazole gel 1% once daily has been shown to exhibit a more rapid onset of therapeutic effect than topical therapy alone \textsuperscript{18}.

Renewed research interest has led to the development of other emerging therapies for rosacea including topical ivermectin, brimonidine and oxymetazoline \textsuperscript{19}. If patients do not respond to various therapies or if they are immunocompromised, the differential diagnosis of demodicosis should be considered; here the treatment is oral ivermectin. Some forms of rosacea (\textit{Rosacea fulminans} and \textit{Granulomatous rosacea}) may be treated initially with oral corticosteroids.

New topical formulation of the acaricidal compound, ivermectin. Although the exact pathophysiology is yet to be elucidated, one well-known hypothesis for the etiology of rosacea is the presence of Demodex mites in the pilosebaceous unit of affected individuals \textsuperscript{20}. Reports have been published on cutaneous demodicidosis responding to oral ivermectin and topical permethrin, but data is lacking on the topical application of ivermectin alone \textsuperscript{21}. When used twice daily with sunscreen, the antiparasitic agent permethrin has been shown to effectively reduce papules and erythema, but not telangiectasias, pustules, and rhinophyma. The use of incobotulinumtoxin A seems a new possibility in rosacea: previous anecdotal evidence in fact suggests botulinum toxin may involve a neuro-
genic component to vascular dysfunction inflammation, and hypersebaceous activity. A newly published article introduces the utility of a new cream based on 5% potassium azeloyl diglycinate and 1% hydroxypropyl chitosan in rosacea stages I and II too. The possibility to modify the molecule of azelaic acid with glycine increases its moisturizing and anti-inflammatory properties. In this study, the Authors demonstrate improvements in redness and hydration as well as in flushing and burning after 4 weeks of use of this product twice daily. Finally, the use of topical K vitamin seems to be useful in rosacea for its anti-inflammatory activity. As is known, this vitamin has been demonstrated an alternative therapy in acneiform reactions induced by inhibitors of epidermal growth factor receptor (anti-EGFR), in particular in rosaceaform dermatitis. Vitamin K is a very potent activator of EGFR suppressing the effect of inhibitors of EGFR. Evidence for these topical agents requires further validation in larger well-controlled studies before they can be recommended for treating rosacea.

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