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Acitretin Induces an Increased Adherence of *S. Aureus* to Epithelial Cells

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Recently, synthetic retinoids have been implicated as causing a rise in the incidence of staphylococcal infections in patients orally treated with these compounds for various disorders of keratinization. Since the adherence of bacteria to epithelia is an important early event in the development of bacterial infections, in the present study we investigated the in vitro effects of acitretin on the adherence of *Staphylococcus aureus* to epithelial cells of the anterior nares of 15 healthy human subjects. It was found that pre-incubation of nasal epithelial cells with acitretin causes a statistically significant ($p < 0.001$) increase in the adherence of *S. aureus* to these cells, as compared to the controls. The growth of *S. aureus* cultures in the presence of acitretin exerted no effect on the staphylococcal adherence. These results suggest that the oral acitretin-induced increase in *S. aureus* colonization and in the incidence of cutaneous staphylococcal infections may be related to the enhancement of staphylococcal adherence to epithelia caused by this compound.

(Accepted January 4, 1989.)

Acta Derm Venereol (Stockh) 1989; 69: 330–332.

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Staphylococcus aureus is a bacterial pathogen of major concern in dermatology since it is the most common cause of cutaneous infections (1). Recently, isotretinoin and etretinate have been implicated as causing an increased colonization of anterior nares by *S. aureus* and a rise in the incidence of staphylococcal infections in patients orally treated with these compounds for various disorders of keratinization (2, 3, 4).

Adherence of bacteria is an important early event in the bacterial colonization of epithelial surfaces and in the pathogenesis of the subsequent infections (5, 6, 7). Furthermore, selective adherence seems to be responsible for species and tissue bacterial tropisms (1).

Since acitretin, the main metabolite of etretinate, shares very similar side-effects with the parent drug (8) in the present study we investigated the in vitro effects of acitretin on the adherence of *S. aureus* to epithelial cells of the anterior nares of healthy human subjects.

MATERIAL AND METHODS

Epithelial suspensions

Epithelial cells were obtained from the anterior nares of 15 healthy volunteers by gently scraping with a wooden tongue depressor and suspended in phosphate buffered saline (PBS: 0.07 M phosphate; 0.15 M NaCl, pH 7.4). More than 95% of the cells were viable, as indicated by their ability to exclude 0.4% trypan blue. For the bacterial adherence assays we used epithelial cells pre-incubated with 450 ng/ml acitretin (in 1% DMSO) for 30 min. In preliminary experiments we found no significant differences between the effects of acitretin in concentrations of 450, 800 and 1 300 ng/ml. Epithelial cells pre-incubated in 1% DMSO without acitretin served as controls.

Bacterial suspensions

A clinical strain of *S. aureus* was grown overnight (18 h) at 37°C in nutrient broth containing 450 ng/ml acitretin. Cultures without acitretin were used as controls. All cultures were then centrifuged, washed and suspended in PBS at a final concentration of 10^8 bacteria/ml.

Bacterial adherence assay

The ability of the test organism to bind to epithelial cells was tested as previously described (9). The epithelial cells were

Table I. *Influence of acitretin on Staphylococcus aureus adherence to nasal epithelial cells in vitro*

Treatment of epithelial cells and *S. aureus* cultures	Adhered Staphylococci/cell ($x \pm SD$)
Pre-incubation of epithelial cells with 1% DMSO and untreated *S. aureus* cultures	19.1 ± 4.1
Pre-incubation of epithelial cells with acitretin	48.8 ± 4.1*
Pre-incubation of *S. aureus* cultures with acitretin	21.3 ± 3.2

* $p < 0.001$.

washed three times and resuspended in PBS to a concentration of 10^5 cells/ml. The bacterial suspensions (0.5 ml) were mixed with an equal volume of epithelial suspensions and rotated for 30 min at 37°C. The cells were then washed three times in PBS to remove unattached bacterial cells. Smears were prepared in duplicate, were stained for 30 sec with crystal violet and examined under bright field microscopy by two different observers. Adherence of *S. aureus* was determined by counting the number of bacteria attached to each epithelial cell. For each experiment, 50 epithelial cells were examined. The obtained results were statistically analysed by the Student's *t*-test.

RESULTS

The results of the present study are summarized in Table I. Pre-incubation of nasal epithelial cells with acitretin caused a statistically significant increase in the adherence of *S. aureus* to these cells, as compared to the controls ($p < 0.001$). In contrast, the growth of *S. aureus* cultures in presence of acitretin failed to exert any significant effects on the staphylococcal adherence to nasal epithelial cells.

DISCUSSION

In the last few years, accumulating evidence indicates that acitretin, the main metabolite of etretinate, is equally effective as the parent drug in the systemic treatment of severe forms of psoriasis and other keratinization disorders (10, 11, 12).

Acitretin is much safer than etretinate for use in women of childbearing potential since its half life time is significantly shorter than that of the latter (13). These two compounds share very similar toxicity patterns, particularly as far as their mucocutaneous side-effects are concerned (8, 14). Thus, the occurrence of *S. aureus* infections of the skin and mucosae in a considerable number of patients receiving oral acitretin for various genodermatoses was not unexpected (unpublished data).

It has been previously suggested, that the pathogenesis of the enhanced staphylococcal colonization of the skin and mucosae and of the predisposition to *S. aureus* infections during treatment with oral retinoids is more likely related to skin fragility and changes in the cutaneous microenvironment (15) than to the immunomodulating effects of these compounds (2). Since it is widely accepted that bacterial adherence is a prerequisite to most colonization and infection processes, in the present investigation we studied the effects of acitretin on the staphylococcal adherence to nasal epithelial cells of healthy human subjects in vitro. It was shown that incubation of the cells with acitretin was capable of inducing a statistically significant increase of *S. aureus* adherence, whereas, growth of the bacteria in the presence of this compound failed to exert any significant effect. Although these in vitro results cannot be directly extrapolated to in vivo conditions, they do suggest that the acitretin-induced increase in *S. aureus* colonization and the incidence of cutaneous staphylococcal infections in orally treated patients may be related to the enhancement of staphylococcal adherence to epithelia, caused by this compound. This hypothesis seems to be supported by the observation that atopic skin reveals an unusual tendency to become colonized and infected by *S. aureus* (16) which exhibits a marked adherence to atopic corneocytes in vitro. The mechanisms by which the effects of acitretin on staphylococcal adherence are mediated remain unknown. Nevertheless, it seems reasonable to assume that this drug may interfere with the structural and functional integrity of receptors for *S. aureus* at the surface of epithelial cells.

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Seborrhoeic Dermatitis and Pityrosporum ovale: A Cultural and Immunological Study

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Seborrhoeic dermatitis is associated with *Pityrosporum ovale*, but the exact role of the organism is not clarified. In order to study this connection we have investigated 30 patients with seborrhoeic dermatitis with quantitative culture for *P. ovale*, serum IgG antibodies against *P. ovale* and lipid measurements. We compared the patients with 60 healthy individuals and found no significant difference in the number of *P. ovale* or serum antibodies. The lipid content on the skin was significantly higher in the patient group ($p=0.0001$). There was no difference in the number of *P. ovale* in lesions compared to healthy skin in the patient group. This study support our theory that an abnormal reaction in the skin to *P. ovale* causes the inflammation and the number of *P. ovale* is of minor importance. *Key words: Antibodies; Lipid content.*

(Accepted January 19, 1989.)

Acta Derm Venereol (Stockh) 1989; 69: 332–335.

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Seborrhoeic dermatitis is characterized by inflammation and desquamation in areas with a rich supply of sebaceous glands, namely the scalp, face and upper trunk. Several studies indicate that *P. ovale* is associated with seborrhoeic dermatitis, but the exact role of the organism in the disease is still unclear (1–4). Many antimycotics have been effective in treatment (5–7) and cure of seborrhoeic dermatitis is often parallelled by a fall in numbers of *P. ovale* (5–7) and recolonization leads to recurrence of seborrhoeic dermatitis (8). Abnormalities in the composition of skin lipids in seborrhoeic dermatitis have been found (9, 10), but no increase in sebum excretion rate (11) or sebum levels (9) has been reported. There have also been reports of high IgG antibodies against *P. ovale* in sera from patients with seborrhoeic dermatitis (2). *P. ovale* is a member of the normal human cutaneous flora (12). The colonization starts during puberty when the sebaceous glands become active (13). *P. ovale* can be found on the skin of almost all adults (14) and the presence of the organism cannot be the only explanation of the disease.

In this investigation, the presence of *P. ovale* on the skin, IgG serum antibodies against *P. ovale* and skin lipid measurements were studied in patients with seborrhoeic dermatitis.