

REFERENCES

1. Haxthausen, H.: Kortfattet lærebog i hud- og kønssygdomme. Munksgaard, Copenhagen, 1950.
2. Lomholt, G.: Syphilis, yaws and pinta. In Textbook of Dermatology (ed. R. Rook, D. S. Wilkinson & F. J. G. Ebling, 1st and 2nd ed. Blackwell Scientific Publications, Oxford and Edinburgh, 1968 and 1972).

Treatment of Acne Vulgaris with Topically Applied Erythromycin and Tretinoin

Otto H. Mills, Jr and Albert M. Kligman

Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Received May 8, 1978

Abstract. A twice daily application of 2% erythromycin base in a hydroalcoholic solution accompanied by once daily use of 0.05% tretinoin (retinoic acid) solution was substantially more effective than tretinoin or erythromycin alone for treatment of inflammatory acne of moderate severity. Therapeutic enhancement by this combination can be attributed to the different modes of action, erythromycin acting chiefly by suppressing *Propionibacterium acnes*, while tretinoin is comedolytic. In addition, by altering the horny layer barrier, tretinoin doubtless increases the penetration of erythromycin.

Key words: Acne vulgaris (inflammatory); Treatment combination; Topically applied erythromycin; Tretinoin

For many years, oral antibiotics, chiefly tetracyclines and erythromycin, have been a mainstay for keeping inflammatory acne under control. Though not beyond argument, the therapeutic benefits derive from the suppression of *P. acnes*, an anaerobe which produces comedogenic substances and various "toxins" that contribute to the rupture of comedones (3).

It was logical to search for bacteriostatic substances that might have the same therapeutic effect by topical application, thus avoiding the risks of systemic use, modest though these have been. This aim was long thwarted. We failed to demonstrate worthwhile improvement with a variety of familiar topical bacteriostats, including the antibiotics chloramphenicol and tetracycline. Insufficient penetration is the likely explanation for the feeble

showing of otherwise potent antimicrobial substances. Most antibiotics in clinical use are in a form very unsuitable for diffusion into skin, that is, they are water-soluble, polar salts (neomycin sulfate, for example). At last we found that 2% erythromycin base in equal parts of water and ethanol was as effective in acne vulgaris as was oral tetracycline (9). Fulton & Pablo (1) had observed that a variety of erythromycins could reduce the free fatty acids (FFA) of the surface lipids when applied topically, the effect being proportional to lipid solubility.

Further experience has convinced us of the feasibility of effectively using topical antibiotics in the management of acne. As expected, existing open and closed comedones are not affected, for antibiotics do not have exfoliant or comedolytic properties. Comedolytic agents interfere with comedo formation by preventing horny cells from sticking tightly together. Tretinoin (Vitamin A acid) is the most powerful of these (8). Since the modes of action of tretinoin and erythromycin differ so completely, the one lessening the cohesiveness of horny cells, the other suppressing bacteria, one can anticipate enhanced therapeutic benefits from the combination of the two. We showed previously that the combination of topical tretinoin and oral tetracycline was more effective than either alone (10).

We now report that this holds equally well for the combination of tretinoin and topical erythromycin.

MATERIAL AND METHOD

Four groups of 20 subjects, each with papulo-pustular acne of moderate severity, were studied. Acne conglobata cases were excluded as well as those with dominantly non-inflammatory, comedonal acne. The average age was 16½ years. There were 45 males and 35 females, 68 whites and 12 blacks.

The first group received 0.05% tretinoin solution (Retin-A® Johnson & Johnson) once daily before retiring. The second applied 2% erythromycin base (ethyl alcohol water, 1:1) once in the morning and again at night. The third group also applied erythromycin twice daily but tretinoin was added just before bedtime. The control group used the ethanol-water vehicle twice daily. The patients washed with a nonmedicated soap (Purpose Soap, Johnson & Johnson) two to three times daily and used no other medication.

The erythromycin solution was prepared freshly every 2 weeks, since the base form is not stable over long periods of time. The patients were seen at 2-week intervals during the 8-week treatment period. Papulo-pustules and comedones were counted on one side of the face at the begin-

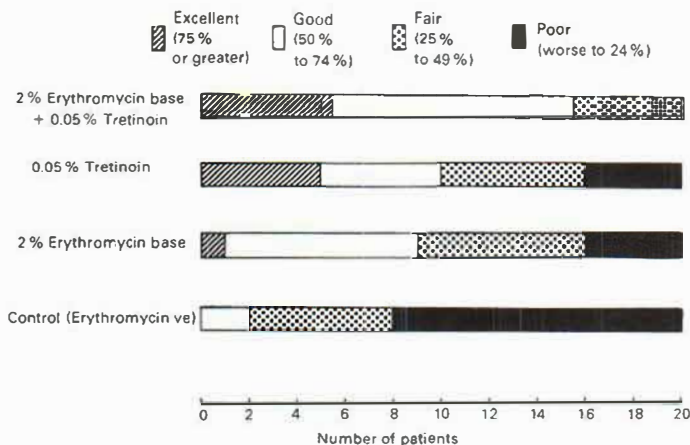


Fig. 1. Clinical effectiveness at eight weeks.

ning and end of 8 weeks. Clinical effectiveness was judged according to our usual scheme: excellent, 75% or more reduction in lesion count; good, 50% to 74%; fair, 25% to 49%; poor, less than 25% or worse.

RESULTS

The differences among the groups can be quickly grasped by considering the percentages of patients experiencing good and excellent results (Fig. 1). By this measure the rank order of effectiveness was: (1) combined treatment (75%), (2) tretinoin (50%), (3) erythromycin (45%), (4) control vehicle (10%). Viewed differently, none of the patients on the combination had a poor result, while one-fifth of those treated with tretinoin or erythromycin alone fell into this category.

DISCUSSION

As expected, the combination was unequivocally superior to either drug alone. The differing actions of the two agents were made strikingly apparent during the four visits of the treatment period. Erythromycin caused no peeling and the comedo count declined only slightly by 8 weeks. Inflammatory lesions, by contrast, were quickly brought under control. By 4 weeks there was unmistakable reduction in the number of papulo-pustules, an effect that greatly pleased and impressed the patients. Erythromycin thus dealt swiftly with the very lesions that especially torment the acne victim. Tretinoin on the other hand ameliorated the prominent disfigurement of the disease, in a slower fashion, the comedolytic effect dominating. Indeed, the

blowing-up of incipient comedones occasionally worsened the appearance during the early weeks of treatment. While tretinoin actually ejects comedones, it also inhibits their formation. Thus, over a longer period, its major action is prophylactic.

While inflammatory lesions are the immediate target of erythromycin, the administration of antibiotics over many months will eventually lead to a decrease in comedones. This accords with the concept that *P. acnes* is intimately involved in inducing comedones. In addition to producing comedogenic substances as such, *P. acnes* produces lipases which split triglycerides to comedogenic free fatty acids (5). Actually, it is only with quite efficacious drugs that one can attempt to form therapeutic judgements in so short a time as 8 weeks. The notorious uncertainties attending therapeutic evaluations are lessened somewhat by longer treatment periods, 3 months generally being a minimum.

Besides striking at different links in the chain of pathogenesis, there is yet another factor which contributes to the greatly enhanced therapeutic effect of the combination. Tretinoin markedly reduces the permeability of skin by weakening the horny layer barrier. The corneocytes become less firmly attached and the number of cell layers decreases by about 50% (2). Thus the penetration of erythromycin—or any other drug, for that matter—will be enhanced. One could say, therefore, that tretinoin potentiates the antimicrobial activity of erythromycin by increasing its tissue concentration. We applied erythromycin separately to avoid the possibility of incompatibility with tretinoin.

This study is only the beginning of our efforts to

manage less severe cases of acne vulgaris of the face by topical means exclusively. Other erythromycin derivatives and other antibiotics should be examined. We see erythromycin base as a prototype illustrating the feasibility of external antibiotic treatment. Many of the good and excellent clinical results seen with topically applied erythromycin occurred in patients who could be characterized as being "fair complexioned". Also, in general, it has been our experience that the more severe cases of acne vulgaris frequently require full dosages of oral antibiotics.

It is perhaps fortunate that erythromycin should be the first topically effective antibiotic in acne. Erythromycin ointment has been on the market for many years. Adverse reactions are exceedingly uncommon. Erythromycin is not an irritant, a contact allergen, or a photosensitizer. So far, after many tests, we have not encountered resistant strains of *P. acnes*; this parallels our experience with oral tetracyclines. The usual objections to topical antibiotics which are also used systemically do not apply to acne vulgaris. *P. acnes* is not a pathogen in the usual sense and it would be of little consequence if it did acquire resistance. Pathogens such as *S. aureus* and β -hemolytic streptococci are not part of the acne microflora (7) nor of the normal cutaneous biotica (6). Hence, there is little danger of inducing resistant strains of virulent bacteria. Unlike *P. acnes*, the resident aerobes do become resistant to erythromycin but it is difficult to imagine what harm can come from that.

In contrast to oral use of erythromycin, we have obtained no proof that topical application substantially decreases the *P. acnes* population (4, 9). The FFA, however, undergo a significant reduction (1, 4) and follicular porphyrin fluorescence also disappears (4). These are signs which unmistakably indicate an effect on the metabolic activities of *P. acnes*.

REFERENCES

1. Fulton, J. E. & Pablo, G.: Topical antibacterial therapy for acne. *Arch Dermatol* 110: 83-86, 1974.
2. Kaidbey, K., Kligman, A. M. & Yoshida, H.: Effects of intensive application of retinoic acid on human skin. *Br J Dermatol* 92: 693-701, 1975.
3. Kligman, A. M.: An overview of acne. *J Invest Dermatol* 62: 268-287, 1974.
4. Kligman, A. M., Mills, O. H., McGinley, K. J. & Leyden, J. J.: Acne therapy with tretinoin in combination with antibiotics. *Acta Dermatovener (Stock-*

holm), Suppl. 74: 111-115, 1975. International Symposium, Flims, January, 1975.

5. Kligman, A. M., Wheatley, V. R. & Mills, O. H.: Comedogenicity of human sebum. *Arch Dermatol* 102: 267-275, 1970.
6. Marples, M.: The Ecology of Human Skin. Charles C. Thomas, Springfield, Ill., 1965.
7. Marples, R. R., Leyden, J. J., Stewart, R., Mills, O. H. & Kligman, A. M.: The skin microflora in acne vulgaris. *J Invest Dermatol* 62: 37-41, 1974.
8. Mills, O. H. & Kligman, A. M.: Assay of comedolytic agents in the rabbit ear. In *Animal Models in Dermatology* (ed. H. Maibach), pp. 176-183. Churchill Livingstone, New York, 1975.
9. Mills, O. H., Kligman, A. M. & Stewart, R.: The clinical effectiveness of topical erythromycin in acne vulgaris. *Cutis* 15: 93-96, 1975.
10. Mills, O. H., Marples R. R. & Kligman, A. M.: Acne vulgaris. Oral therapy with tetracycline and topical vitamin A acid. *Arch Dermatol* 106: 200-203, 1972.

Pediculosis Capitis Treated with Quassia Tincture

O. Jensen, A. Otkjær Nielsen and
P. Bjerregaard

*Department of Dermatology, Municipal Hospital,
Copenhagen, Denmark*

Received May 20, 1978

Abstract. 454 patients were treated with quassia tincture for head lice. At examination one week later only three patients had hatched lice. There was firm evidence that these patients had been reinfested. The treatment procedure was acceptable both to patients and to staff and no side-effects were observed. As resistance to clophenothane has appeared, alternative cures are needed. This study confirms earlier reports on the effectiveness of quassia tincture, which seems to be a useful alternative to clophenothane. At present the recommended treatment is two applications with an interval of one week.

Key words: Pediculosis capitis; Quassia tincture

During recent years we have noticed increasing numbers of patients with head lice and, among these, a large proportion who were not cured by our then current treatment with preparations of clophenothane.

Therefore a change of treatment was considered. We decided to resume the treatment with quassia tincture, which was introduced for the treatment of