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ACNE THERAPY WITH TRETINOIN IN COMBINATION WITH ANTIBIOTICS

Albert M. Kligman, Otto H. Mills, Kenneth J. McGinley and James J. Leyden

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

Three drugs have put into the hands of modern therapists an effective means of moderating acne vulgaris. In order of their appearance these are: 1) oral antibiotics, 2) benzoyl peroxide, and 3) tretinoin (retinoic acid). These agents are supplanting ancient medicaments which are frequently noxious and also of questionable efficacy. Before discussion of combination therapy, one must first review the mode of action of each agent. Existing knowledge, while incomplete, does afford some insights and rationale for the use of combinations.

Oral antibiotics

Tetracyclines are the prototype, having been in use for over twenty years. Erythromycin is equally effective. Clindamycin is the newest addition to the list, though questions are arising concerning its safety for long-term use. While most would declare without hesitation that antibiotics are helpful because they suppress the growth of bacteria, a nagging doubt persists that antibiotics may exert therapeutic effects in some different way. The question arises because most acne patients can be controlled with one-quarter to one-half the dose required for soft tissue infections. Then there is also the uncertainty concerning the role of bacteria in the pathogenesis of acne vulgaris.

Nonetheless, we find irresistible evidence for an etiological role for *Propionibacterium acnes* (*Corynebacterium acnes*). This anaerobic diphtheroid almost exclusively occupies the depths of sebaceous follicles where comedones commence. Surface aerobic cocci, mainly *Staphylococcus epidermis* cannot be implicated. They are too superficially located to instigate comedone formation. Moreover, during antibiotic therapy these organisms, while initially suppressed, rapidly develop resistance and remain as a stable population (8). On the other hand, antibiotics keep the *P. acnes* population at a low level (10).

P. acnes, however, is not a pathogen in the usual sense. It remains viable only in the follicular lumen and dies rapidly on injection into the dermis. Acne is not an infection. We conceive that *P. acnes* plays two roles and both are indirect. First of all, this organism participates in the creation of comedones (4). Masses of *P. acnes* accumulate in follicles in the initial stages of comedo formation, forming "sebaceous filaments". The latter can be expressed as soft cheesy, whitish "worms" and are virtually pure growths of *P. acnes*. One can extract lipoid substances from sebaceous filaments as well as from cultured cells, which are highly comedogenic (5). These lipids rapidly induce large comedones in the external ear canal of the rabbit. Secondly, the rupture of comedones is almost certainly dependent on the presence of large numbers of *P. acnes*. Various metabolic products, especially proteases, disrupt the epithelial lining of comedones, allowing the contents to escape into the dermis. There the horny cells and lipids, especially free fatty acids (FFA) incite a toxic abscess with huge numbers of neutrophils spreading far into the tissue (4). Pustules and inflammatory lesions are not secondary infections; bacteria extruded into the dermis at the time of rupture die quickly. Comedones which lack a population of *P. acnes*, for example those provoked by coal tars, have little tendency to rupture, as phenolic substance in the tar restrains the growth of *P. acnes*. Furthermore, injection of *P. acnes* into keratinous cysts induces rupture of the cyst wall and the development of an inflammatory lesion (3).

Turning now to the mode of action of oral antibiotics, it can be shown that the effective ones always possess three actions: 1) *P. acnes* is decreased by 90% or more, 2) the proportion of FFA in the surface lipid falls approximately 50%, and 3) the coral red fluorescence of the follicles disappears. The

fluorescence is due to porphyrins elaborated by *P. acnes* (1). Reduction of *P. acnes* will of course automatically engender a fall in both FFA and porphyrins. Effective antibiotics accumulate in the follicle via holocrine excretion, i.e. by being incorporated in keratinizing cells which then transport the drug to the follicular lumen. Holocrine excretion does not occur with penicillin or sulfonamides which, as a result, are useless in the therapy of acne (8).

Dermatologists have discovered that antibiotics control acne at one-half to one-quarter the usual dose. Our studies provide evidence to support this practice. *P. acnes* and FFA can be lowered to practically identical levels with one-quarter doses, the only difference being the longer time required to achieve maximum reduction. The customary practice of starting with full doses and lowering to a maintenance level is eminently rational.

We may now examine the magnitude of the responses to full doses of the two antibiotics which are most often used in acne, tetracycline and erythromycin (Fig. 1A, B). The two drugs have identical effects. Clinical experience indicates that they are therapeutically equivalent too. The changes are comparatively slow, being significantly greater at four weeks than at two. The FFA decrease to about 50% of their original value by four weeks. A 90% reduction in the *P. acnes* level occurs by that time and porphyrin fluorescence is barely detectable in most cases.

It is important to note that antibiotics produce such clear-cut effects mainly in individuals with high *P. acnes* counts. In adolescence, it is mainly acne patients who harbor large quantities of *P. acnes* and whose follicles, therefore, fluoresce brightly (7). After age 25, the density of *P. acnes* in normals reaches the same level exhibited much earlier by acne patients (7). Normal adults who show bright fluorescence are therefore suitable subjects for demonstrating antibacterial effects.

Finally it is important to note that *P. acnes* does not develop resistance to antibiotics, even after years of therapy. We have searched diligently for strains of *P. acnes* that are resistant to tetracycline and erythromycin, and to date have found none.

Benzoyl peroxide

Peroxides have long been known to be antibacterial. Benzoyl peroxide came to be extensively used in acne when manufacturers found a way to prepare stable formulations. The effects of benzoyl peroxide are qualitatively the same as systemic antibiotics (Fig. 1D). However, both the speed and the magnitude of the responses are greater. Particularly noteworthy is the virtual eradication of *P. acnes* after two weeks of therapy. FFA reduction occurs faster, but the ultimate decrease is not much greater than with antibiotics, namely about 50%. There are corresponding decreases in the amount of follicular fluorescence. This description applies to 5% benzoyl peroxide formulations applied twice daily. Swifter and even greater reductions can be achieved with twice daily use of 10% formulations.

We have assessed the ability of benzoyl peroxide to exfoliate comedones induced in the external ear of the rabbit by acnegenic substances. The term comedolytic describes this property. Daily application of either 5 or 10% benzoyl peroxide for two weeks reduces the size of ear comedones by about 50%.

Benzoyl peroxide then is both antibacterial and comedolytic, the first action being the more powerful one. It is unique in this regard. Theoretically benzoyl peroxide alone should be as effective as various combinations but this has not been our experience.

Retinoic acid

This is a versatile drug which has numerous pharmacologic actions (6). Its usefulness in acne mainly depends on two of these: 1) cell attachments are lessened; horny cells therefore cannot stick together to form solid impactions. Hence, comedo formation is curtailed, a very important effect since all inflammatory lesions in acne spring from comedones; and 2) retinoic acid stimulates mitotic activity. The turnover of cells lining the follicular epithelium is accelerated, increasing the rate of production of horny cells. These quickly separate from each other and fall apart in a loose mass. The anchorage of existing comedones is thus weakened. The increased flow of horny cells causes closed comedones to be transformed into open ones. In addition, open comedones become extruded.

In the rabbit ear assay, comedones are completely eliminated after two weeks of once daily application of tretinoic. Likewise, the ability of retinoic acid to eliminate human comedones is impressive in all varieties—solar comedones, comedones provoked be X-rays and acnegenic substances, nevus comedonicus, etc. The comedolytic efficacy of tretinoin is unrivaled.

It is exceedingly important to distinguish between "peeling" effects and comedolytic activity. Through-

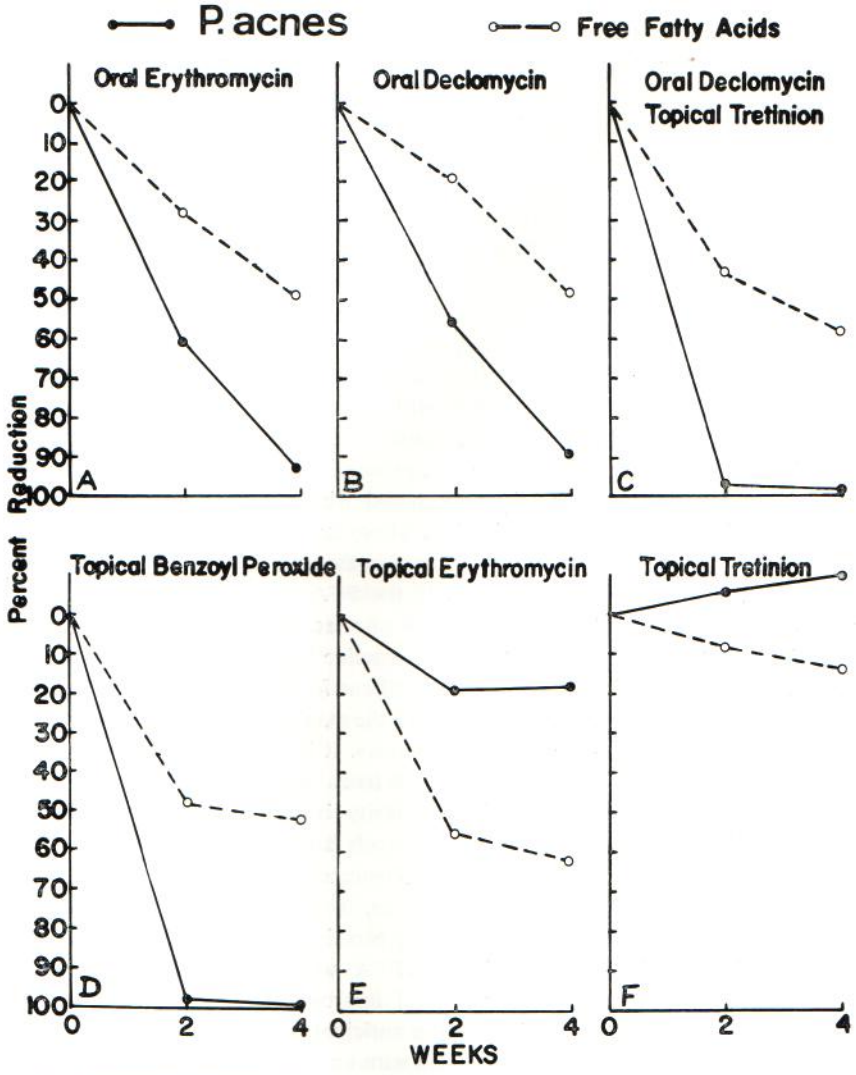

Fig. 1. The effect of various oral and topical therapies on the reduction of *P. acnes* and free fatty acids. Oral antibiotics, erythromycin and declomycin produce significant reductions by 4 weeks. The addition of topical tretinoin results in significant reductions by 2 weeks. Benzoyl peroxide produces highly significant reductions in both *P. acnes* and FFA in 2 weeks. Erythromycin only slightly reduces *P. acnes* counts but causes highly significant reductions in FFA.

out written history, topical remedies have always been "peelers". Peeling or scaling, is a non-specific response to injury and follows in the wake of any inflammatory change. All irritating chemicals cause peeling. Of the many venerable ones that have been used in acne, few have had the ability to exfoliate comedones. Among those which lack appreciable comedolytic activity are resorcinol, phenol, beta-naphthol, and sulfur. The latter is actually comedogenic. All these accelerate epidermal cell turnover and create, thereby, visible scaling. However, they apparently do not reach the key target, the follicular epithelium. It is essential that "peeling" occur at this deep level. While some irritants may possess comedolytic activity, all comedolytic agents are irritants and thus have to be used with caution. It should be emphasized that irritation is not central to the comedolytic activity of drugs like benzoyl peroxide or retinoic acid. Lower concentrations that are virtually free of irritation can be used if one is willing to wait longer for realization of beneficial effects. We ourselves advise vigorous therapy, using scaling and erythema as a guide to dosage.

One effect common to all irritants should be mentioned since it accounts for the willingness to believe in the efficaciousness of various and sundry peeling

agents. All these tend to promote the resorption of papulopustular lesions. The latter usually take about ten days to heal without treatment. Peeling agents may reduce this time by half. Patients, of course, perceive the effect. Sulfur seems to dry up inflammatory lesions especially well. We think it likely that irritants mainly enhance resorption by stimulating blood flow (cryotherapy and ultraviolet light act similarly). Nonetheless, "peelers" that are neither antibacterial nor comedolytic have little justification.

Peeling agents are described as having a "drying" action as well, the implication being that sebum production is decreased. The appearance of oiliness is, in fact, decreased but this is a visual artifact due to scaling. Decreased sweating also makes the skin look less oily. The sebum level remains the same with the "peelers" we have studied: sulfur, retinoic acid, benzoyl peroxide and resorcinol.

The daily application for one month of "peeling" doses of retinoic acid has no significant effect on either FFA or *P. acnes* (Fig. 1F). In various studies we have made, there may be some fluctuation, but the changes have never been significant. Fluorescence, as expected, did not change. The value of retinoic acid thus rests on its considerable comedolytic activity by which it impedes the formation of comedones and eliminates those already present. It may be mentioned in passing that the occasional outcropping of pustules in a few weeks after starting therapy is due to the rupture of preexisting invisible microcomedones, a desirable even if sometimes alarming effect.

Oral tetracycline and topical retinoic acid

Since these drugs act in entirely different ways, greater effectiveness can be expected from the combination than with either one alone. We evaluated three groups of patients. The first received 0.05% retinoic acid solution (Retin A, Johnson & Johnson); the second received demeclocycline (Declomycin, Lederle) 600 mg daily for three weeks and 300 mg therafter; the third was treated with a combination of the two.

The quickest way to grasp the differences in effectiveness of the three treatments is to examine what proportion of patients in each group achieved good to excellent results, that is, more than 50% reduction in the total lesion count. Sixty-seven percent of patients receiving combined therapy had good to excellent results while the comparative figures were 48% for retinoic acid alone and 41% for demeclocycline. Further, about 35% of the combination patients were rated excellent in comparison to about 10% for either drug alone. Improvement was noted earlier with the combination, a matter of no little importance in encouraging diligent drug usage.

The effects on the quantity of *P. acnes* and the proportion of FFA are shown in Fig. 1C.

As regards *P. acnes*, retinoic acid, had no effect, of course. With demeclocycline a significant reduction in the *P. acnes* population occurred by the fourth week while with the combination there was already a ten-fold reduction by two weeks. By eight weeks, *P. acnes* was reduced by about 95% with demeclocycline, compared with more than 99% with the combination. Thus, the latter effected a swifter and greater decrease in the quantity of *P. acnes*.

Changes in the FFA paralleled the decreases in the population of anaerobes. Retinoic acid had no effect. Demeclocycline brought about a decrease of about 45% in about four weeks. A 50% reduction in FFA is about the maximum with acne-suppressing doses of antibiotics. It is important to note that the decrease in FFA had already occurred by two weeks. This time disparity between the early decline of FFA and the much later reduction in *P. acnes* is a characteristic phenomenon (see below).

To summarize, combination therapy has the following easily perceived effects: earlier and greater reductions in FFA and *P. acnes*, and swifter and greater clinical improvement. This is the pattern which can be anticipated when comedolytic agents are combined with an anti-microbial drug.

Enhanced therapeutic effectiveness can be explained quite simply. In short term studies such as these the differing effect of the two agents quickly comes to light. Retinoic acid prevents or expels comedones by its action on keratinizing cells, while the main thrust of the antibiotic is to limit the production of products of *P. acnes*, namely those which are comedogenic or which have toxic effects (proteases, lipases) and thus promote the rupture of comedones.

Over and above these disparate actions, one can submit that retinoic acid indirectly augment the efficacy of the antibiotic. The erythema produced by retinoic acid is a sign of increased vascular permeability. It is well known that the tissue concentration of circulating drugs is increased at sites where the skin is inflamed. Thus, more antibiotic will be de-

livered to the interstitial fluid compartment of the dermis. Additionally, the retinoic acid induced acceleration in cell turnover of the follicular epithelium will inevitably allow more of the antibiotic to be transported into the canal, the habitat of *P. acnes*. It can be said that the retinoic acid promotes the delivery of the antibiotic to the very sites where it is needed.

Topical erythromycin

It has recently been demonstrated by us and by Fulton et al. (2) that topical erythromycin (the base, not water-soluble, polar salts) is effective in the treatment of acne. We have used 2% erythromycin base in equal parts of ethanol and water. We consider the therapeutic effect to be at least as great as with oral antibiotics. It is noteworthy that other antibiotics to which *P. acnes* is extremely susceptible were either ineffective viz. chloramphenicol, or only modestly helpful, tetracyclines for example. In our experience topical erythromycin achieves a speedier clinical improvement than do full doses of oral antibiotics.

It was thus a matter of compelling interest to determine the effect of topical erythromycin on the quantity of *P. acnes* and the FFA. The results were surprising, to say the least (Fig. 1E). Most notable was the slight effect on the density of *P. acnes*. In several experiments there was a consistent decrease which, however, never amounted to more than about 20%, a trivial change and not significant. Paradoxically, the FFA and the porphyrin fluorescence diminished considerably, the former to a degree paralleling benzoyl peroxide—in short, rather impressively. On the face of it, the findings are contradictory. It is incontestable that both fluorescence and the FFA level are dependent on the quantity of *P. acnes*. How can one account for decreases in both of these without a significant reduction in *P. acnes*? It is necessary here to make a distinction between suppressing multiplication of the organism and inhibiting the production of certain products. Mates has found that concentrations of antibiotics which are not inhibitory to growth may still suppress the synthesis of lipases (9). Metabolic inhibition, in short, can be attained without killing the organism.

This seems a plausible explanation for the paradoxical action of topical erythromycin. It does not kill *P. acnes* but it apparently interferes with the capacity of the organism to elaborate lipases, porphyrins and other products which contribute to the pathogenesis of acne.

Recently we have found that 2% clindamycin base has effects comparable to erythromycin.

Topical erythromycin and tretinoin

This combination offers the following advantages: tretinoin is directly beneficial through its comedolytic action. It also enhances the penetration of topical erythromycin by producing a thinner stratum corneum. At the present time, these agents must be used separately and not be combined physically, in order to avoid incompatability problems. Once daily use of tretinoin combined with once or twice daily topical application of 2% erythromycin produces clinical improvement comparable to tretinoic and systemic antibiotics (11). Current studies are under way to evaluate the effects on FFA and *P. acnes*. Preliminary results indicate that the combination produces both a swifter fall and a greater reduction in FFA than does topical erythromycin used alone. Likewise, a more rapid clinical improvement occurs.

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