METHODS OF TREATING ACNE

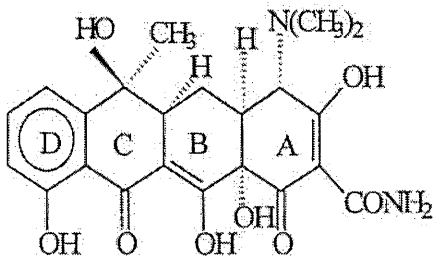
BACKGROUND OF THE INVENTION

Acne is a common inflammatory disease in skin areas where sebaceous glands are largest, most numerous, and most active. In its mildest form, acne is a more or less superficial disorder characterized by slight, spotty skin irritations. In such cases, ordinary skin hygiene is typically a satisfactory treatment. In the more inflammatory types of acne, however, pustules; infected cysts; and in extreme cases, canalizing, inflamed and infected sacs appear. Without effective treatment, these lesions may become extensive and leave permanent, disfiguring scars.

Micro-organisms, especially *Propionibacterium acnes*, are strongly implicated in the pathogenesis of acne. The micro-organisms are thought to release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes.

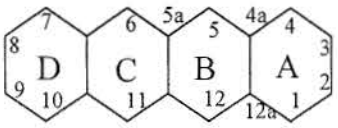
Accordingly, the efficacy of antibiotics in treating acne is thought to be due, in significant part, to the direct inhibitory effect of the antibiotics on the growth and metabolism of these micro-organisms. Systemically-administered tetracycline antibiotics, especially minocycline hydrochloride, are particularly effective in treating acne.

The tetracyclines are a class of compounds of which tetracycline is the parent compound. Tetracycline has the following general structure:



Structure A

The numbering system of the multiple ring nucleus is as follows:



Structure B

Tetracycline, as well as the 5-OH (oxytetracycline, e.g. Terramycin) and 7-Cl (chlorotetracycline, e.g. Aureomycin) derivatives, exist in nature, and are all well known antibiotics. Semisynthetic derivatives such as 7-dimethylamino-tetracycline (minocycline) and 6α-deoxy-5-hydroxy-tetracycline (doxycycline) are also known tetracycline antibiotics. Natural tetracyclines may be modified without losing their antibiotic properties, although certain elements of the structure must be retained to do so.

In addition to the direct antimicrobial activity of tetracyclines, further activities of antibiotic tetracyclines have been investigated for possible therapeutic effects on acne.

For example, a study by Elewski et al., *J. Amer. Acad. Dermatol.*, *8*:807-812 (1983) suggests that acne therapy, consisting of orally-administered tetracycline at a total daily dose of 1000mg, may have therapeutic anti-inflammatory effects in addition to antimicrobial effects. In particular, it was found that tetracycline inhibited neutrophil chemotaxis induced by bacterial chemotactic factors.

However, a more recent study performed by Eady et al., *J. Invest. Dermatol.*, *101*:86-91 (1993) found somewhat different results with respect to the effect of tetracyclines on cytokines. The study was designed to determine whether oral acne therapy with minocycline or tetracycline altered the cytokine content of open comedones. The total daily dose of minocycline administered was 100mg. The total daily dose of tetracycline administered was 1000mg. It was found that these therapies upregulated the production of bioactive IL-1α-like material and immunochemical IL-1β. IL-1 is considered to be a pro-inflammatory cytokine. The authors speculate that increased levels

of IL-1 in comedones destined to become inflamed may enhance resolution and promote repair of the damaged follicular epithelium.

Another possible activity of tetracyclines in acne therapy was investigated by Bodokh, I., et al., *Acta. Derm. Venerol.*, *77*:255-259 (1997). Their study was designed to evaluate the action of minocycline on sebaceous excretion in acne patients. A 100mg daily dose of minocycline was administered. A subclinical increase in seborrhoea was reported. The authors propose that minocycline induces an increase in seborrhoea via a reduction in ductal obstruction. The mechanism by which the ductal obstruction is reduced is proposed to be the reduction in ductal irritation. The authors suggest that the reduction of ductal irritation is due to minocycline's direct effect on *P. acnes*, or minocycline's effect on the lipase produced by *P. acnes*.

Bodokh et al. also found that during treatment no correlation exists between seborrhoea intensity and clinical severity of acne. The authors state that the lack of correlation shows that seborrhoea is pathogenic because it is the "culture medium" of *P. acnes*. Thus, it can be concluded that the authors consider the antimicrobial activity of minocycline as a significant therapeutic activity with respect to acne.

Similarly, in a recent clinical study it was found that tetracycline doses lower than antimicrobial doses had no clinical effect on acne. (Cunliffe et al., *J. Am. Acad. Dermatol.*, *16*:591-9 (1987).) In particular, a 100mg total daily dose of minocycline; and a 1.0g total daily dose of tetracycline were found to be necessary to successfully treat acne.

The antimicrobial effects of antibiotics are generally directly proportional to the dose administered of the antibiotics. Accordingly, in moderate to severe (i.e. inflammatory) forms of acne, oral antibiotics are typically administered at high doses. For example, in conventional acne therapy, tetracycline is administered at an initial dose of 500 to 2,000 mg/day, followed by a maintenance dose of 250-500 mg/day.

Clearly, the state-of-the-art teaching is that the clinical efficacy of systemically-administered tetracyclines in the treatment of acne is due in significant part to the antimicrobial effects of the tetracyclines.

The use of tetracycline antibiotics, however, can lead to undesirable side effects. For example, the long term administration of antibiotic tetracyclines can reduce or eliminate healthy microbial flora, such as intestinal flora, and can lead to the production of antibiotic resistant organisms or the overgrowth of yeast and fungi. Other side effects include gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, rashes, and other allergic reactions. Tetracyclines also can cause fetal harm if used during pregnancy.

Accordingly, there is a need for an effective treatment of acne which does not cause the undesirable side effects produced by the systemically-administered antibiotics used in conventional acne therapy.

SUMMARY OF INVENTION

The present invention provides a method of treating acne in a human in need thereof. The method comprises administering systemically to the human a tetracycline compound in an amount that is effective to treat acne but has substantially no antimicrobial activity, without administrating a bisphosphonate compound.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the photoirritancy factor (PIF) for some tetracycline compounds. For structure K, the compounds indicated are as follows:

COL	R7	R8	R9
308	hydrogen	hydrogen	amino
311	hydrogen	hydrogen	palmitamide
306	hydrogen	hydrogen	dimethylamino

For structures L, M, N or O the compounds indicated are as follows:

COL	R7	R8	R9
801	hydrogen	hydrogen	acetamido
802	hydrogen	hydrogen	dimethylaminoacetamido
804	hydrogen	hydrogen	nitro
805	hydrogen	hydrogen	amino

For structure P, R7 is hydrogen, R8 is hydrogen and R9 is nitro.

DETAILED DESCRIPTION

The present invention provides methods of treating acne. As used herein, the term "acne" is a disorder of the skin characterized by papules, pustules, cysts, nodules, comedones, and other blemishes or skin lesions. These blemishes and lesions are often accompanied by inflammation of the skin glands and pilosebaceous follicles, as well as, microbial, especially bacterial, infection.

For the purposes of this specification, acne includes all known types of acne Some types of acne include, for example, acne vulgaris, cystic acne, acne atrophica, bromide acne, chlorine acne, acne conglobata, acne cosmetica, acne detergicans, epidemic acne, acne estivalis, acne fulminans, halogen acne, acne indurata, iodide acne, acne keloid, acne mechanica, acne papulosa, pomade acne, premenstral acne, acne pustulosa, acne rosacea, acne scorbutica, acne scrofulosorum, acne urticata, acne varioliformis, acne venenata, propionic acne, acne excoriee, gram negative acne, steroid acne, and nodulocystic acne.

The present invention can also be used to treat certain other types of acneiform dermal disorders, e.g. perioral dermatitis, seborrheic dermatitis in the presence of acne, gram negative folliculitis, sebaceous gland dysfunction, hiddradenitis suppurativa, pseudo-folliculitis barbae, or folliculitis.

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