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(54) METHODS OF TREATING ACNE

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(57) ABSTRACT

A method of treating acne in a human in need thereof comprising administering systemically to said human a tetracycline compound in an amount that is effective to treat acne but has substantially no antibiotic activity, without administering a bisphosphonate compound.

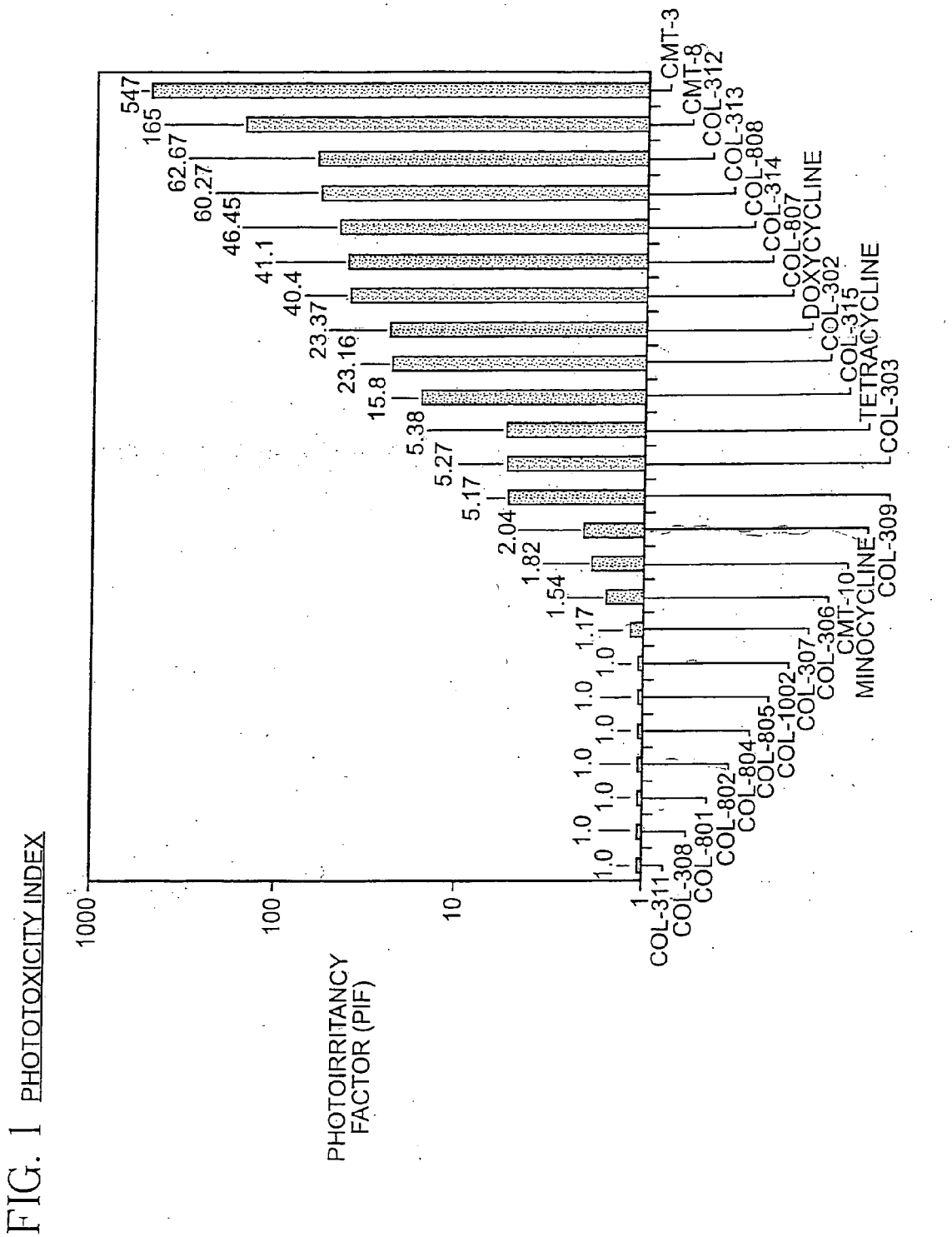


FIG. 1

METHODS OF TREATING ACNE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 60/281,916, filed Apr. 5, 2001, and U.S. Provisional Application No.60/325,489, filed Sep. 26, 2001, both of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Acne is a common disease characterized by various types of lesions. The areas affected typically are areas of the skin where sebaceous glands are largest, most numerous, and most active. The lesions associated with acne are usually categorized as either non-inflammatory or inflammatory.

[0003] Non-inflammatory lesions include comedones. Comedones appear in two forms, open and closed. Comedones are thought to arise from abnormal follicular differentiation. Instead of undergoing shedding and discharge through the follicular orifice, abnormal desquamated cells (keratinocytes) become unusually cohesive, forming a microcomedo or a microscopic hyperkeratotic plug in the follicular canal. The progressive accumulation of these microcomedones lead to visible comedones.

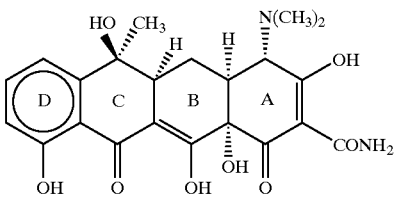
[0004] In its mildest form, acne is a more or less superficial disorder characterized by slight, spotty skin irritations. In such cases, ordinary skin hygiene is typically a satisfactory treatment. In the more inflammatory types of acne, however, pustules; infected cysts; and in extreme cases, canalizing, inflamed and infected sacs appear. Without effective treatment, these lesions may become extensive and leave permanent, disfiguring scars.

[0005] Microorganisms, especially *Propionibacterium acnes*, are strongly implicated in the pathogenesis of acne. The microorganisms are thought to release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes.

[0006] 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 microorganisms. Systemically-administered tetracycline antibiotics, especially minocycline hydrochloride, are particularly effective in treating acne.

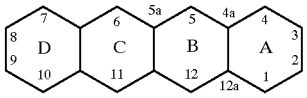
[0007] The tetracyclines are a class of compounds of which tetracycline is the parent compound. Tetracycline has the following general structure:

Structure A



[0008] The numbering system of the multiple ring nucleus is as follows:

Structure B



[0009] Tetracycline, as well as the 5-hydroxy (oxytetracycline, e.g. Terramycin) and 7-chloro(chlorotetracycline, e.g. Aureomycin) derivatives, exist in nature, and are all well known antibiotics. Semisynthetic derivatives such as 7-dimethylaminotetracycline(minocycline) and 6α-deoxy-5-hydroxytetracycline(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.

[0010] In addition to the direct antibiotic activity of tetracyclines, further activities of antibiotic tetracyclines have been investigated for possible therapeutic effects on acne.

[0011] 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 1000 mg, may have therapeutic anti-inflammatory effects in addition to antibiotic effects. In particular, it was found that the anti-inflammatory effect of tetracycline was, at least in part, due to inhibition of neutrophil chemotaxis induced by bacterial chemotactic factors.

[0012] A more recent study, performed by Eady et al., *J. Invest. Dermatol.,* 101:86-91 (1993), evaluated the effects of oral minocycline or tetracycline therapy on the cytokine and microflora content of open comedones in acne patients. The total daily dose of minocycline administered was 100 mg. The total daily dose of tetracycline administered was 1000 mg.

[0013] Eady et al. found that the therapies upregulated the production of bioactive IL-1α-like material and immunochemical IL-1β. IL-1 is considered to be a pro-inflammatory cytokine.

[0014] Accordingly to Eady et al., no overall decrease in the numbers of propionibacteria/mg of comedonal material was found. It is important to note, however, that the numbers of propionibacteria/mg of comedonal material are not expected to decrease in response to antibiotic therapy. Since the bacteria within comedones are encapsulated by the follicle, they are not susceptible to antibiotic treatment.

[0015] 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 100 mg 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 a reduction in ductal irritation. The authors suggest that the reduction of ductal irritation is due to

[0016] 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 antibiotic activity of minocycline to be therapeutically significant with respect to acne.

[0017] Similarly, in a recent clinical study it was reported that tetracycline in sub-antibiotic doses had no clinical effect on acne. (Cunliffe et al., *J. Am. Acad. Dermatol.,* 16:591-9 (1987).) In particular, a 100 mg total daily dose of minocycline and a 1.0 g total daily dose of tetracycline were found to be necessary to successfully treat acne.

[0018] The antibiotic 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.

[0019] Clearly, the state-of-the-art teaching is that the clinical efficacy of systemically-administered tetracyclines in the treatment of acne is due, at least in significant part, to the antibiotic effects of the tetracyclines. In addition to their antibiotic effects, it has been proposed that tetracyclines reduce the number of inflammatory lesions (papules, pustules and nodules) by a variety of non-antibiotic mechanisms. Such mechanisms include interfering with the chemotaxis of polymorphonuclear leukocytes (PMN) into the inflammatory lesion, inhibition of PMN derived collagenase, and by scavenging reactive oxidative species produced by resident inflammatory cells.

[0020] There is no disclosure in the prior art of using either a sub-antibiotic dose of an antibiotic tetracycline compound, or of using a non-antibiotic tetracycline compound for the treatment of acne.

[0021] 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.

[0022] Accordingly, there is a need for an effective treatment of acne which causes fewer undesirable side effects produced by the systemically-administered antibiotics used in conventional acne therapy.

SUMMARY OF INVENTION

[0023] 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 antibiotic activity (i.e. substantially no antimicrobial activity), without administering a bisphosphonate compound.

[0024] Additionally, the present invention provides methods for reducing the number of comedones, inhibiting oxi-

These methods comprise administering systemically to the human a tetracycline compound in an amount that is effective for its purpose, e.g., to reduce the number of comedones, to inhibit oxidation of melanin, and/or to inhibit lipid-associated abnormal follicular differentiation, but has substantially no antibiotic activity.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] **FIG. 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

[0026] 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

[0027] For structure P, R8 is hydrogen and R9 is nitro.

DETAILED DESCRIPTION

[0028] 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.

[0029] 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 scorbutica, acne scrofulosorum, acne urticata, acne varioliformis, acne venenata, propionic acne, acne excoriee, gram negative acne, steroid acne, nodulocystic acne and acne rosacea. Acne rosacea is characterized by inflammatory lesions (erythema) and permanent dilation of blood vessels (telangectasia).

[0030] The present invention is particularly effective in treating comedones, e.g., reducing the number of comedones. Both open and closed comedones can be treated in accordance with the methods of this invention.

[0031] The present invention can also be used to treat

acne, gram negative folliculitis, sebaceous gland dysfunction, hiddradenitis suppurativa, pseudo-folliculitis barbae, or folliculitis.

[0032] The method comprises the administration of a tetracycline compound to a human in an amount which is effective for its purpose e.g., the treatment of acne, including reducing the number of comedones, but which has substantially no antibiotic activity.

[0033] The tetracycline compound can be an antibiotic or non-antibiotic compound. The tetracycline compound has the general tetracycline structure indicated above, or a derivative thereof.

[0034] Some examples of antibiotic (i.e. antimicrobial) tetracycline compounds include doxycycline, minocycline, tetracycline, oxytetracycline, chlortetracycline, demeclocycline, lymecycline and their pharmaceutically acceptable salts. Doxycycline is preferably administered as its hyclate salt or as a hydrate, preferably monohydrate.

[0035] Non-antibiotic tetracycline compounds are structurally related to the antibiotic tetracyclines, but have had their antibiotic activity substantially or completely eliminated by chemical modification. For example, non-antibiotic tetracycline compounds are capable of achieving antibiotic activity comparable to that of tetracycline or doxycycline at concentrations at least about ten times, preferably at least about twenty five times, greater than that of tetracycline or doxycycline, respectively.

[0036] Examples of chemically modified non-antibiotic tetracyclines (CMTs) include 4-de(dimethylamino)tetracycline (CMT-1), tetracyclinonitrile (CMT-2), 6-demethyl-6-deoxy-4-de(dimethylamino)tetracycline (CMT-3), 7-chloro-4-de(dimethylamino)tetracycline (CMT-4), tetracycline pyrazole (CMT-5), 4-hydroxy-4-de(dimethylamino)tetracycline (CMT-6), 4-de(dimethylamino-12α-deoxytetracycline (CMT-7), 6-deoxy-5α-hydroxy-4-de(dimethylamino)tetracycline (CMT-8), 4-de(dimethylamino)-12α-deoxyanhydrotetracycline(CMT-9), 4-de(dimethylamino)minocycline (CMT-10).

[0037] Further examples of chemically modified non-antibiotic tetracyclines include Structures C-Z. (See Index of Structures.)

[0038] Tetracycline derivatives, for purposes of the invention, may be any tetracycline derivative, including those compounds disclosed generically or specifically in co-pending U.S. patent application Ser. No. 09/573,654 filed on May 18, 2000, which are herein incorporated by reference.

[0039] The minimal amount of the tetracycline compound administered to a human is the lowest amount capable of providing effective treatment of acne. Effective treatment is a reduction or inhibition of the blemishes and lesions associated with acne. The amount of the tetracycline compound is such that it does not significantly prevent the growth of microbes, e.g. bacteria.

[0040] Two ways in which to describe the administered amount of a tetracycline compound is by daily dose, and by serum level.

[0041] For example, tetracycline compounds that have [illegible] preferably, the antibiotic tetracycline compound is administered in a dose which is 40-70% of the antibiotic dose.

[0042] Some examples of antibiotic doses of members of the tetracycline family include 50, 75, and 100 mg/day of doxycycline; 50, 75, 100, and 200 mg/day of minocycline; 250 mg of tetracycline one, two, three, or four times a day; 1000 mg/day of oxytetracycline 600 mg/day of demeclocycline; and 600 mg/day of lymecycline.

[0043] Examples of the maximum non-antibiotic doses of tetracyclines based on steady-state pharmacokinetics are as follows: 20 mg/twice a day for doxycycline; 38 mg of minocycline one, two, three or four times a day; and 60 mg of tetracycline one, two, three or four times a day.

[0044] In a preferred embodiment, to reduce the number of comedones, doxycycline is administered in a daily amount of from about 30 to about 60 milligrams, but maintains a concentration in human plasma below the threshold for a significant antibiotic effect.

[0045] In an especially preferred embodiment, doxycycline hyclate is administered at a 20 milligram dose twice daily. Such a formulation is sold for the treatment of periodontal disease by CollaGenex Pharmaceuticals, Inc. of Newtown, Pa. under the trademark Periostat®.

[0046] Example 38 below summarizes a clinical study using 20 mg doxycycline hyclate tablets administered twice a day. A significant reduction in the number of comedones was observed. This reduction in the number of comedones is unexpected. The reduction is particularly unexpected since, as can be seen from the microbiology results in Example 38, the treatment with doxycycline resulted in no reduction of skin microflora vis-à-vis a placebo control.

[0047] The administered amount of a tetracycline compound described by serum levels follows.

[0048] An antibiotic tetracycline compound is advantageously administered in an amount that results in a serum tetracycline concentration which is 10-80% of the minimum antibiotic serum concentration. The minimum antibiotic serum concentration is the lowest concentration known to exert a significant antibiotic effect.

[0049] Some examples of the approximate antibiotic serum concentrations of members of the tetracycline family follow.

[0050] For example, a single dose of two 100 mg minocycline HCl tablets administered to adult humans results in minocycline serum levels ranging from 0.74 to 4.45 μg/ml over a period of an hour. The average level is 2.24 μg/ml.

[0051] Two hundred and fifty milligrams of tetracycline HCl administered every six hours over a twenty-four hour period produces a peak plasma concentration of approximately 3 μg/ml. Five hundred milligrams of tetracycline HCl administered every six hours over a twenty-four hour period produces a serum concentration level of 4 to 5 μg/ml.

[0052] In one embodiment, the tetracycline compound can be administered in an amount which results in a serum concentration between about 0.1 and 10.0 μg/ml, more preferably between 0.3 and 5.0 μg/ml. For example, doxycycline is administered in an amount which results in a [illegible]

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