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REPUBLICATION

(54) **METHOD FOR THE TREATMENT OF ACNE**

(75) Inventors: **Mitchell Wortzman**, Scottsdale, AZ (US); **R. Plott**, Briscoe, TX (US); **Kuljit Bhatia**, Nesconset, NY (US); **Bhiku Patel**, Chandler, AZ (US)

Correspondence Address:
KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614 (UNITED STATES)

(73) Assignee: **Medicis Pharmaceutical Corporation**, Scottsdale, AZ (US)

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(57) **ABSTRACT**

A method for treatment of acne with tetracyclines is provided. A lower sustained dose and no loading dose is employed, with an optional once-a-day dosing regimen.

METHOD FOR THE TREATMENT OF ACNE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. application Ser. No. 11/166,817 filed on Jun. 24, 2005 the entire disclosure of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] This invention relates to the treatment of acne vulgaris, commonly known simply as "acne." Acne is a disease of the skin in which the pilosebaceous structures of the skin become inflamed, leading to the formation of comedones, pustules and nodules. Acne can lead to permanent scarring in severe cases.

[0003] It is generally believed that acne arises when hyperkeratosis of the pilosebaceous structure wholly or partially blocks the opening of the structure, resulting in comedones filled with sebum, keratin, and *Propionibacterium acnes*. These lesions are commonly identified as acne. *P. acnes* naturally occurs in normal skin, but is especially and characteristically present in acne lesions. It is believed that metabolic byproducts and waste from *P. acnes* within the pilosebaceous structures cause or contribute to the inflammation of acne lesions.

[0004] Conventional acne treatments have taken many forms. Topical keratolytic agents, such as salicylic acid are sometimes used. Keratolytic agents are thought to encourage the opening up of blocked pilosebaceous structures, thereby reducing conditions that are favorable to inflammation. Benzoyl peroxide, an anti-microbial, remains a popular and effective treatment. Topical antibiotics, such as clindamycin, which are effective against *P. acnes*, have also been used with a view towards preventing the formation of metabolic byproducts from this organism. Topical retinoids such as tretinoin have also been used in the treatment of acne.

[0005] Systemic (i.e. non-topical) treatments for acne include the use of oral antibiotics in more serious cases. These treatments are directed towards the reduction in the amount *P. acnes* in the skin, especially the pilosebaceous structures, and seek to reduce the inflammation caused by waste materials and metabolic byproducts from these organisms. Tetracycline antibiotics are most commonly used for this purpose. These include tetracycline, minocycline and doxycycline. Erythromycinis also sometimes used.

[0006] Standard oral minocycline therapy for acne in pediatric patients calls for the administration of a 4 mg/kg initial loading dose, and a 2 mg/kg dose every 12 hours thereafter. This results in a dose of 6 mg/kg on the first day of treatment and a 4 mg/kg dose each day thereafter. In adults, a 200 mg initial dose is followed by a 100 mg dose every 12 hours thereafter. In a typical patient, this results in about a 4.5 mg/kg dose on the first day of treatment, and 3.0 mg/kg dose each day thereafter.

[0007] In cases where acne does not respond to oral antibiotic treatment, oral isotretinoin is sometimes used. While effective, isotretinoin is also powerfully teratogenic, and women of childbearing age are required to use multiple methods of contraception while taking the drug.

[0008] While oral tetracycline antibiotics remain a highly favored and widely used treatment for more serious cases of acne, it is not without side effects. Vestibular side effects, including extreme dizziness and concomitant nausea, can be so severe as to result in discontinuance of tetracycline therapy. Long term use can sometimes result in vaginal candidisis, esophageal erosions and in antibiotic resistant infections.

[0009] Some recent research has indicated that very low doses of oral tetracycline can result in some improvement of acne even though the dose of tetracycline is too low to have an antibiotic effect. This observation has been attributed to an anti-inflammatory effect of tetracycline compounds. This effect has been reported to have been observed even where a chemically modified tetracycline that have no antibiotic properties are used. The use of tetracycline antibiotics at a dose too low to have an antibiotic effect or the use of modified tetracycline having no antibiotic properties as treatments for acne has never been approved by any drug regulatory agency.

SUMMARY OF THE INVENTION

[0010] According to the present invention, a method is provided for the treatment of acne in which an antibiotically effective dose of an oral tetracycline, such as minocycline, is provided. This dose is approximately 1 milligram per kilogram of body weight (1 mg/kg), without an initial loading dose of antibiotic. This antibiotic dosing regimen has been found to be as effective as a conventional dosing regimen incorporating a significant initial loading dose and higher subsequent doses. However, the dosing method of the current invention produces far fewer side effects.

[0011] In another aspect of this invention, the oral tetracycline is provided in a dosage form that provides for the continued release of the antibiotic between doses, as opposed to an immediate or nearly immediate release of the drug.

DETAILED DESCRIPTION OF THE INVENTION

[0012] According to the present invention, acne vulgaris is treated by the use of an oral tetracycline antibiotic, preferably minocycline. This antibiotic is administered in an antibiotically effective amount of approximately 1.0 milligram per kilogram of body weight per day (1.0 mg/kg/day). While this may be accomplished by the use of divided doses, it is preferred that the tetracycline antibiotic be delivered in a single daily dose. This treatment regime is initiated without a loading dose, and is continued until resolution or substantial resolution of the patient's acne. The course of treatment typically lasts 12 to up to 60 weeks, but will be adjusted according to the disease status and other medical conditions of each patient in the exercise of ordinary good clinical judgment by the patient's health care provider.

[0013] Controlled, double-blinded studies were undertaken to determine the effectiveness of this invention. Treatment of

473 patients with acne was undertaken according to the present invention. Placebos were provided to 239 patients. The effectiveness of the invention in treating acne vulgaris is shown in Table 1.

TABLE 1

	Total Lesion Counts	
	Total Lesions	Total Lesions (as Percent of Baseline)
Baseline (mean)	169.3	100
Day 28 (mean)	134.0	78
Day 56 (mean)	119.3	69
Day 84 (mean)	112.3	66
	Inflammatory Lesion Counts	
	Inflammatory Lesions	Inflammatory Lesions (as Percent of Baseline)
Baseline (mean)	77.4	100
Day 28 (mean)	52.1	66
Day 56 (mean)	44.3	56
Day 84 (mean)	41.9	53

[0014] While effective as a treatment for acne, this resulted in almost no side effects above those observed with a placebo, as shown in Table 2.

TABLE 2

	% Subjects with Adverse Events	
	Minocycline	Placebo
At least One Adverse Event	56.2	54.1
At Least One Serious Adverse Event	0.4	0
Blood/Lymphatic System Disorders	0.3	0.3
Cardiac Disorders	0.3	0
Ear and Labyrinth Disorders	3.6	3.3
Endocrine Disorders	0.3	0
Eye Disorders	2.2	2.7
Gastrointestinal Disorders	21.2	26.1
General Disorders and Administrative Site Conditions	13.8	10.4
Immune System Disorders	0.7	2.5
Infections and Infestations	9.3	11.0
Laboratory Blood Abnormalities	0.7	1.1
Metabolism and Nutrition Disorders	0.6	0.3
Musculoskeletal and Connective Disorders	4.6	3.6
Neoplasms Benign, Malignant and Unspecified	0.1	0
Nervous System Disorders	29.2	25.8
Psychiatric Disorders	6.4	7.1
Renal and Urinary Disorders	0.3	0.5
Reproductive System and Breast Disorders	0.7	0.3
Respiratory, Thoracic and Mediastinal Disorders	5.3	6.9
Skin and Subcutaneous Tissue Disorders	8.6	7.1
Vascular Disorders	1.0	0.3

[0015] The effectiveness of this invention can be seen by comparing the above efficacy data with published data on the effectiveness of conventional tetracycline treatments for acne in the reduction of total acne lesions and in the reduction of inflammatory lesions. See, e.g. Hersel & Gisslen, "Minocycline in Acne Vulgaris: A Double Blind Study," Current Therapeutic Research, 1976.

[0016] Because of the variations in body weight encountered in clinical practice, in the actual practice of this invention it is not practical to provide every patient with exactly 1 mg/kg/day of oral tetracycline antibiotic. However, it is acceptable to approximate this dose by providing the patient with from 0.5 to 1.5 mg/kg/day although from 0.7 to 1.3 mg/kg/day is preferred, and 1.0 mg/kg/day is ideal.

[0017] While it can be effective to provide the oral tetracycline antibiotic in divided doses taken over the course of a day (e.g. twice or three times a day), it is preferable to provide the oral tetracycline antibiotic in a dosage form that releases the antibiotic slowly during the course of a day so that once-a-day dosing is possible. While delayed release dosage forms are known in the art, the formulation of them is far from predictable and the selection of a specific delayed release formulation is accomplished more by trial and error than by mathematical prediction based on known properties of delay release agents. No delayed release product useful in the present invention has been known heretofore.

[0018] It has been discovered that the ratio of fast dissolving carriers to slow dissolving carriers in the core caplet is important in obtaining a dissolution profile that enables once-a-day dosing in accordance with the present invention. By keeping the ratio of these components within a certain range, one may obtain this result.

[0019] The fast dissolving carrier is any binder, vehicle, or excipient that quickly dissolves in an aqueous physiological medium, such as gastric fluid, thereby tending to quickly release the active ingredient. Lactose, its salts and hydrates are good examples of such components. It has been observed that sometimes a portion of the fast dissolving components are formulated in a manner that results in the complete or partial encapsulation or inclusion or coating of these fast-dissolving materials in granules of slow-dissolving materials. These encapsulated materials are excluded from the calculation of the above mentioned ratio of fast-dissolving to slow dissolving components.

[0020] A slow dissolving carrier is any binder, vehicle, or excipient that dissolves slowly over the course of hours and perhaps a day, thereby slowing the release of the active ingredient. Examples of such components are polyvinyl pyrrolidone, polyvinyl acetate, microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or waxy or lipid-based tableting agents such as magnesium stearate or calcium stearate. Outer "enteric" coatings are excluded from this amount when calculating the above-mentioned ratio.

[0021] Insoluble carriers are binders, vehicles, or excipients that are practically insoluble in physiological fluids, such as gastric fluid, and includes compounds, such as silicon dioxide and talc.

[0022] While the exact formulation of these dosage forms can vary, it has been observed that it is advantageous to formulate them so that the ratio of fast dissolving carriers to slow dissolving carriers is from 0.30 to 0.50, and preferably from 0.35 to 0.45. A ratio of about 0.36 to 0.40 is particularly preferable.

[0023] Dosage forms, such as capsules, tablets, and caplets that release 25 to 52% of the antibiotics within 1 hour, 53 to 89% in 2 hours, and at least 90% within 4 hours are suited to the once-a-day dosage regimen contemplated by the current inventories. More preferably, 30 to 52% of the antibiotic is released within 1 hour, 53 to 84% within 2 hours, and at least 85% within 4 hours.

[0024] Alternatively, the oral tetracycline antibiotic may be delivered in a dosage form that releases the antibiotic in such a way that the maximum blood concentration of the antibiotic (C_{max}) is reached at about 3.5 hours after administration (T_{max}). In actual practice of the invention, the C_{max} should be reached between 2.75 and 4.0 after administration, more preferably between 3.0 and 3.75 after administration.

[0025] As examples of such a once-a-day formulation, one may use the following:

Component	Quantity (mg)
135 mg Caplet	
Minocycline (as hydrochloride) (dry weight)	145.8
Lactose Monohydrate (intragranular)	107.4
Lactose Monohydrate (extragranular)	43.8
Total Lactose Monohydrate	151.2
HPMC	94
Silicon Dioxide	3
Mg. Stearate	6
45 mg Caplet	
Minocycline (as hydrochloride) (dry weight)	48.6
Lactose Monohydrate (intragranular)	192.2
Lactose Monohydrate (extragranular)	42.2
Total Lactose Monohydrate	234.40
HPMC	108
Silicon Dioxide	3
Mg. Stearate	6

[0026] Each of these components is combined in a conventional fashion, compressed in a tabletting apparatus, and then provided in a conventional manner with a suitable coating, such as, without limitation Opadry II and optional coloring.

What is claimed is:

1-5. (canceled)

6. An oral dosage form, comprising:

an antibiotically effective dose of an oral minocycline; and

a pharmaceutically suitable delivery vehicle;

wherein said oral dosage form is for administration once daily to provide a patient with about 0.5 mg/kg/day to about 1.5 mg/kg/day of said oral minocycline; and

wherein said oral dosage form provides a continuous slow release, without a loading dose, of said oral minocycline, at a release rate in gastric fluid of either about 25% to about 52% within about 1 hour, about 53% to about 89% within about 2 hours, and at least about 90% within about 4 hours, or about 30% to about 52% within about 1 hour, about 53% to about 84% within about 2 hours, and at least about 85% within about 4 hours.

7. The oral dosage form of claim 6, wherein said oral minocycline is minocycline as hydrochloride.

8. The oral dosage form of claim 6, wherein said oral dosage form is for administration once daily to provide said patient with about 1.0 mg/kg/day of said oral minocycline.

9. An oral dosage form, comprising:

an antibiotically effective dose of an oral minocycline; and

a pharmaceutically suitable delivery vehicle;

wherein said oral dosage form is for administration once daily to provide a patient with about 0.5 mg/kg/day to about 1.5 mg/kg/day of said oral minocycline; and

wherein said oral dosage form does not provide an immediate release of said oral minocycline, and provides a continuous slow release, without a loading dose, of said oral minocycline at a rate so that C_{max} is reached at about 3.5 hours after administration to said patient.

10. The oral dosage form of claim 9, wherein said oral minocycline is minocycline as hydrochloride.

11. The oral dosage form of claim 9, wherein said oral dosage form is for administration once daily to provide said patient with about 1.0 mg/kg/day of said oral minocycline.

12. An oral dosage form, comprising:

an antibiotically effective dose of an oral minocycline;

a fast dissolving carrier; and

a slow dissolving carrier, wherein said fast dissolving carrier and said slow dissolving carrier are at a weight ratio of about 0.3 to about 0.5 that provides a continuous, slow release, without immediate release, of said oral minocycline; and

wherein said oral dosage form is for administration once daily to provide a patient with about 0.5 mg/kg/day to about 1.5 mg/kg/day of said oral minocycline.

13. The oral dosage form of claim 12, wherein said oral minocycline is minocycline as hydrochloride.

14. The oral dosage form of claim 12, wherein said weight ratio of fast dissolving carrier to slow dissolving carrier is 0.35 to 0.45.

15. The oral dosage form of claim 14, wherein said weight ratio of fast dissolving carrier to slow dissolving carrier is 0.36 to 0.40.

16. The oral dosage form of claim 12, wherein said oral dosage form is for administration once daily to provide said patient with about 1.0 mg/kg/day of said oral minocycline.

17. The oral dosage form of claim 12, further comprising an intragranular fast dissolving carrier.

18. The oral dosage form of claim 17, wherein said slow dissolving carrier encapsulates said intragranular fast dissolving carrier.

19. The oral dosage form of claim 18, further comprising a coating.

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