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(54) **COMPOSITIONS AND METHODS FOR TREATING OPHTHALMIC AND OTIC INFECTIONS**

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/577,262, filed as application No. PCT/US99/22622 on Sep. 29, 1999.
(60) Provisional application No. 60/102,504, filed on Sep. 30, 1998, and provisional application No. 60/102,506, filed on Sep. 30, 1998.

(51) **Int. Cl.**[7] **A61K 31/353**

(52) **U.S. Cl.** **514/230.05**; 514/912
(58) **Field of Search** 514/230.05, 912

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,174,878 B1 * 1/2001 Camache et al. 514/211.12

FOREIGN PATENT DOCUMENTS

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(57) **ABSTRACT**

Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues. The compositions and methods of the invention are particularly useful in the treatment of acute otitis externa infections and ophthalmic infections attributable to one or both of two newly identified Microbacterium species, *Microbacterium otitidis* and *Microbacterium alconae*.

6 Claims, 1 Drawing Sheet

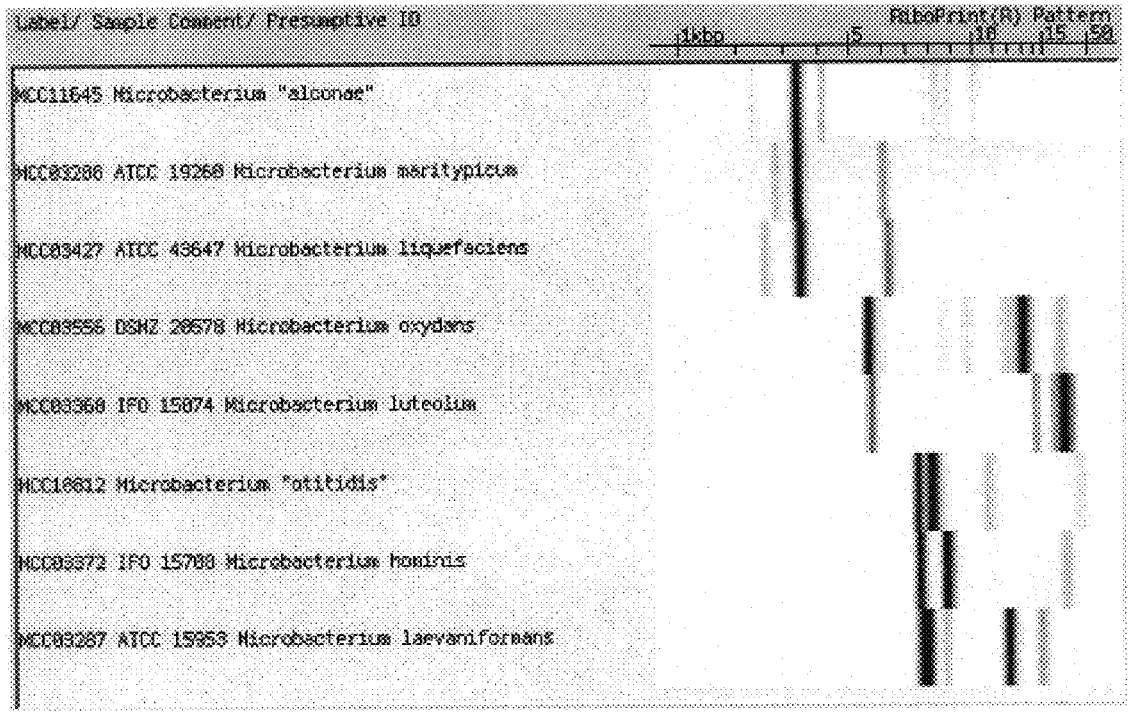


Figure 1

COMPOSITIONS AND METHODS FOR TREATING OPHTHALMIC AND OTIC INFECTIONS

The present application is a continuation-in-part of U.S. application Ser. No. 09/577,262 filed May 19, 2000, which is a 371 of International Application No. PCT/US99/22622 filed on Sep. 29, 1999, which U.S. Provisional Application Ser. No. 60/102,504 and 60/102,506 filed on Sep. 30, 1998.

BACKGROUND OF THE INVENTION

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

Quinolone antibiotics have been previously utilized to treat ophthalmic and otic infections. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution, and a topical otic composition containing a combination of ciprofloxacin and hydrocortisone is marketed by Alcon Laboratories, Inc. under the name CIPRO™ HC. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

Quinolone	Product	Manufacturer
Ofloxacin	OCUFLOX ™	Allergan
Norfloxacin	CHIBROXIN ™	Merck
Lomefloxacin	LOMEFLOX ™	Senju

Ofloxacin has also been utilized to treat otic infections.

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics. Although ciprofloxacin has proven to be an effective agent in treating otic infections, there is a need for a better understanding of the etiology of these infections and a corresponding need for therapies that address the causes of these infections more directly and effectively.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic

otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

SUMMARY OF THE INVENTION

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the use of these antibiotics prior to surgery to sterilize the surgical field and prophylactically following surgery or other trauma to ophthalmic, otic or nasal tissues to minimize the risk of infection. The compositions of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgical procedures to prevent or alleviate post-surgical infection. As utilized herein, the terms "treat", "treating" and derivations thereof are intended to include both treatments of existing infections and treatments to prevent or reduce the risk of infections.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacyrocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

Examples of otic conditions that may be treated with the compositions of the present invention include otitis extema and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

The compositions and methods of the present invention are particularly useful in the treatment of acute infections of the external ear canal, which are commonly referred to as "acute otitis extema" or "AOE". The present invention is based in part on the isolation of two bacterial species that have not previously been identified as pathogens relative to acute otitis externa infections. These bacterial species, which have been named *"Microbacterium otitidis"* and *"Microbacterium alconae"*, are described in greater detail below. The present invention is also based in part on a finding that the antibiotics utilized in the present invention, particularly Moxifloxacin, have a very high level of antimicrobial activity against these newly discovered pathogens, and therefore are particularly useful in the treatment of acute otitis externa infections involving these pathogens.

The two bacterial species that have been identified as being associated with acute otitis extema infections have

also been discovered to be associated with ophthalmic infections. As indicated above, the antibiotics utilized in the present invention have a high level of antimicrobial activity against these newly discovered ophthalmic pathogens, and as a result, the compositions of the present invention are particularly useful in treating ophthalmic infections involving these species.

The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions.

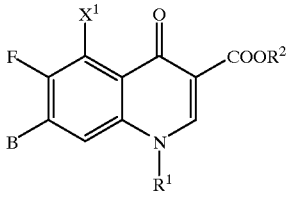
BRIEF DESCRIPTION OF THE DRAWING

The sole FIGURE of drawings is an automated ribotyping chart showing the relationships between two newly identified bacterial species and other, known species.

DETAILED DESCRIPTION OF THE INVENTION

The antibiotics used in the compositions and methods of the present invention have the following formula:

(I)



wherein:

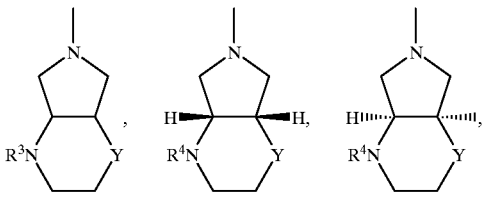
A is CH, CF, CCl, C—OCH_3, or N;

X^1 is H, halogen, NH_2, or CH_3;

R^1 is C_1 to C_3 alkyl, FCH_2CH_2, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R_1 together can form a bridge of formula C—O—CH_2—$CH(CH_3)$;

R^2 is H, C_1 to C_3 alkyl (optionally substituted by OH, halogen or NH_2), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is a selected from the group consisting of:



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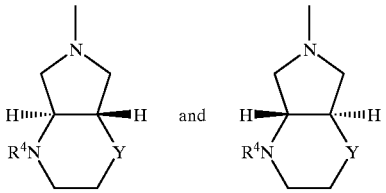


wherein:

Y is O or CH_2;

R^3 is C_2–C_5 alkoxyl, CH_2—CO—C_6H_5, $CH_2CH_2CO_2R'$, $R'O_2C$—CH═C—CO_2R',

CH═CH—CO_2R' or CH_2CH_2—CN,

wherein:

R' is H or C_1 to C_3 alkyl;

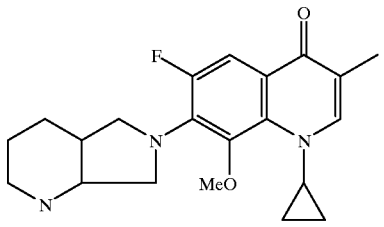
R^4 is H, C_1 to C_3 alkyl, C_2‘C_5 alkoxyl, CH_2—CO—C_6H_5, $CH_2CH_2CO_2R'$,

$R'O_2C$—CH═C—CO_2R', CH═CH—CO_2R', CH_2CH_2—CN or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

wherein:

R' is H or C_1 to C_3 alkyl; and their pharmaceutically useful hydrates and salts.

The compound Moxifloxacin is most preferred. Moxifloxacin has the following structure:



Further details regarding the structure, preparation, and physical properties of Moxifloxacin and other compounds of formula (I) are provided in U.S. Pat. No. 5,607,942. The contents of U.S. Pat. No. 5,607,942 relating to the structure, physical properties, and preparation of the compounds of formula (I) are hereby incorporated in the present specification by reference.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the “minimum inhibitory concentration” or “MIC”. The term “MIC_{90}” refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the “minimum bactericidal concentration” or “MBC”. The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:

Microorganism	MIC_{90}
S. aureus/methicillin sensitive	0.13
S. aureus/methicillin resistant	4.0
S. aureus/quinolone resistant	4.0
S. epidermidis/methicillin sensitive	0.25
S. epidermidis/methicillin resistant	4.0
S. pneumoniae/penicillin sensitive	0.25
S. pneumoniae/penicillin resistant	0.25
P. aeruginosa	8.0
H. influenzae/β-lactamase positive	0.06
H influenzae/βlactamase negative	0.06
M. otitidis	2.0
M. alconae	0.25

All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

As indicated above, the present invention is based in part on the identification of two bacterial species that are believed to act as pathogens in acute otitis externa infections, *Microbacterium otitidis* and *Microbacterium alconae*. These bacteria belong to the class known as "coryneforms" or "diphtheroids". Bacteria belonging to this class have been previously identified as being present both in healthy ears and in ears afflicted with acute otitis externa infections. However, prior to the present invention, there had been no species-level identification of the coryneform bacteria present either in healthy ears or infected ears, nor had there been any attempt to eradicate the pathogenic species present in acute otitis externa infections with antibiotic therapy keyed to those species. The present inventors have now identified two species of coryneform bacteria as being present in acute otitis externa infections, and have determined that the compounds of formula (I), particularly Moxifloxacin, are very effective in eradicating these species.

Microbacterium otitidis and *Microbacterium alconae* have also been discovered to be pathogens in infections of ophthalmic tissues, such as conjunctivitis and blepharitis. The compositions of the present invention are therefore particularly useful in treating ophthalmic infections involving one or both of these species.

The bacterial species referred to above were identified as a result of research conducted on specimens obtained from 2,122 ears afflicted with acute otitis extema infections and 82 healthy ears. Coryneform bacteria of some type were isolated from 10 to 30% of these ears overall; the incidence of finding this class of bacteria present varied depending on the season when the specimen was taken. Although coryneform bacteria have been identified previously in both healthy and infected ears, the present inventors have discovered that the coryneform bacteria present in healthy ears and in acute otitis externa ears are different. In the acute otitis extema ears, 80% of the coryneform bacteria identified belong to the genus Microbacterium, while in the healthy ears, 90% of is the coryneform bacteria identified belong to the genus Turicella.

The present inventors have also discovered that the coryneform bacteria found in acute otitis externa patients include two species that have not previously been identified. These species are now identified as Microbacterium sp. nov. *otitidis* and Microbacterium sp. nov. *alconae*. These names for the species have been assigned by the inventors, but have not yet been officially published. The names utilized for these species below are *"Microbacterium otitidis"* (sometimes abbreviated as *"M. otitidis"*) and *"Microbacterium alconae"* (sometimes abbreviated as *"M. alconae"*), respectively.

In two thirds of the cases where *M. otitidis* or *M. alconae* isolates were identified as being present, these species were the only type of bacteria recovered. Moreover, these species were not recovered from healthy ears. These findings lead to the conclusion that *M. otitidis* and *M. alconae* are pathogens in acute otitis externa. That is, these species were either largely or totally responsible for the acute otitis externa infections in the ears from which they were isolated. The above-cited findings are believed to represent the first frequent association of the genus Microbacterium with a human infectious disease, namely, acute otitis externa. The two new Microbacterium species that have been discovered to be pathogens in acute otitis externa are described in greater detail below.

Both new species can be distinguished from the 27 recognized species of Microbacterium phenotypically and genetypically. Genetypically, *M. otitidis* is most closely related to *M. hominis*, while *M. alconae* is most closely related to *M. maritypicum* and *M. liquefaciens*.

The two new Microbacterium species have been characterized for taxomonic purposes using DNA methods as well as phenotypic methods. The sequencing of the 16S rRNA gene showed that both sets of strains belonged to the genus Microbacterium, although the sequence differences from established Microbacterium species were significant enough to suggest novel species. Automated ribotyping patterns further clarified the relationships (similarities and differences) with known Microbacterium species. These relationships are shown in FIG. **1**. The above-cited analyses support the categorization of these bacteria as new species.

Both species of Microbacterium grow optimally at 28–30° C. The *M. otitidis* isolates grow up to 37° C., while the *M. alconae* isolates grow up to 35° C. The optimal growth temperature at 28–30° C. is typical for bacteria that are normally found in water and soil.

Phenotypically, the *M. otitidis* isolates are most easily distinguished from *M. hominis* by their inability to metabolize: 1) N-acetyl-D-glucosamine, 2) 3-methyl glucose, 3) alaninamide, or 4) L-serine. The isolates of *M. alconae* can be distinguished from *M. liquefaciens* by their ability to metabolize: 1) amygdalin, 2) D-mannitol, 3) D-melezitose, 4) palatinose, 5) D-psicose, 6) salicin, 7) D-sorbitol, 8) D-xylose, or 9) p-hydoxyphenyl acetic acid. Also, *M. alconae* can be distinguished from *M. maritypicum* by their ability to metabolize: 1) amygdalin or 2) D-xylose, and can be distinguished from *M. maritypicum* by their inability to metabolize: 1) L-fucose.

Analysis of cellular fatty acids for the *M. otitidis* isolates showed the three major fatty acids to be: 1) 17:0 anteiso-60%, 2) 15:0 anteiso-26%, and 3) 16:0 iso-11%. Analysis of the *M. alconae* isolates showed the three major fatty acids to be: 1) 15:0 anteiso-55%, 2) 17:0 anteiso-23%, and 3) 16:0 iso-11%.

The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC_{90} level for the selected antibiotic (s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC_{90} level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as "an

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