Activity of CEM-101, a Novel Fluoroketolide, Tested Against Invasive Isolates of *N. meningitidis* from a Worldwide Collection

F1-2038

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ICAAC 2009

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Abstract

Background: Colonization of the nasopharynx (NP) by *N. meningitidis* (NM) can lead to invasive meningococcal disease. Chemoprophylaxis is used to eradicate NP colonization and prevent transmission to nonimmune contacts. This study evaluated the activity of CEM-101 against invasive clinical isolates of NM.

Methods: 62 isolates (91.9% from blood culture) were collected from 29 medical centers in North and South America and Europe (1997-2008). Strains were tested for susceptibility (S) to CEM-101 and 10 comparators, including β-lactams, fluoroquinolones (FQs), macrolides and three other drug classes, by the CLSI broth microdilution methods. Serological identification was performed for serogroups (SGs) B, C, Y and W-135.

Results: S to penicillin was 82.3% with no resistant (R) strains detected. All isolates were S to ceftriaxone, azithromycin, minocycline and rifampin. Isolates were S to FQs (≤0.015 µg/ml); however 13 strains have been reported to have reduced S to nalidixic acid (MIC ≥8 µg/ml), which may correlate with diminished S to FQs. R to trimethoprim/sulfamethoxazole (TMP/SMX) was 59.7%. Of the MLS_B class agents, CEM-101 was the most active (MIC_{90} of ≤0.015 µg/ml) compared to telithromycin (0.03 µg/ml), azithromycin and clarithromycin (0.12 µg/ml), and erythromycin (0.25 µg/ml). The prevalence rates (%) of SGs were C (41.7), B (38.3), Y (16.7) and W-135 (3.3).

Conclusions: CEM-101 was the most active MLS_B agent tested against NM strains (all MICs ≤0.06 µg/ml) with a potency 2 to ≥16-fold greater than other agents in the class. CEM-101 was active against NM isolates non-S to β-lactams and TMP/SMX. Further studies should determine if CEM-101 can eradicate NM from the NP of at-risk patients in cases where R to other agents (FQ) has emerged.

Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% Susc.[a]	% Res.[a]
CEM-101	≤0.015	≤0.015	≤0.015-0.06	-[b]	-
Telithromycin	≤0.015	0.03	≤0.015-0.12	-	-
Azithromycin	0.06	0.12	≤0.015-0.12	100.0	-
Clarithromycin	0.03	0.12	≤0.015-0.25	-	-
Erythromycin	0.12	0.25	0.03-0.5	-	-
Penicillin	0.03	0.12	≤0.015-0.25	82.3	0.0
Ceftriaxone	≤0.015	≤0.015	≤0.015	100.0	-
Ciprofloxacin	≤0.008	≤0.008	≤0.008-0.015	100.0	0.0
Levofloxacin	≤0.008	≤0.008	≤0.008-0.015	100.0	0.0
Minocycline	0.12	0.12	≤0.008-0.25	100.0	-
Rifampin	0.015	0.06	≤0.008-0.12	100.0	0.0
TMP/SMX[c]	0.5	2	≤0.06-4	37.1	59.7

a. Susceptibility criteria based upon the CLSI (M100-S19, 2009).
b. Susceptibility criteria have not yet been proposed, but azithromycin at ≤2 µg/ml is considered susceptible.
c. Trimethoprim/sulfamethoxazole.

Introduction

Neisseria meningitidis is a bacterial pathogen that is associated with a wide range of human diseases, including significant infections such as fulminant bacteremia and meningitis. The onset and progression of severe meningococcal infections is often rapid with significant morbidity and mortality. In developing countries, conservative mortality rates have been estimated at 10%, and in the United States numerous reports of endemic and epidemic disease have been documented.

Meningococcal isolates have the capacity to spread rapidly from person to person, usually in populations of young people such as high school and college students or military recruits. Transient, intermittent or persistent asymptomatic nasopharyngeal carriage of *N. meningitidis* has been estimated to occur among older children and young adults at rates up to 20%.The pathogenic serogroups are typically encapsulated (polysaccharide capsule) and serogroups A, B, C, Y and W-135 are currently the dominant pathogenic serogroups. The Advisory Committee on Immunization Practices has recommended that adolescents receive the tetravalent polysaccharide or conjugate meningococcal vaccine. However, individuals that have not been vaccinated and those colonized with serogroups not included in the vaccine are at risk of infection and/or spreading infection to non-immune individuals.

In the past, meningococci have been considered to be uniformly susceptible to penicillin, cephalosporins and fluoroquinolones. However, penicillin-resistant and fluoroquinolone-resistant strains of *N. meningitidis* have emerged. A recent report has documented the emergence of ciprofloxacin-resistant *N. meningitidis* in North America, which has been confirmed by the Centers for Disease Control and Prevention. Appropriate antimicrobial chemotherapy and prophylaxis are needed to prevent the spread of pathogenic isolates, including resistant clones associated with outbreaks.

CEM-101 is a novel fluoroketolide agent with enhanced ribosomal binding, that demonstrates potent activity against pathogens resistant to MLS_B agents due to methyltransferase or efflux mechanisms. This study was performed to determine the activity of CEM-101 and comparison agents when tested against a global collection of *N. meningitidis* isolates, including those with reduced susceptibility to penicillin and quinolones (nalidixic acid ≥8; 13 strains).

Materials and Methods

A collection of 62 *N. meningitidis* isolates from the SENTRY Program were collected from 29 participating medical centers in 14 countries located in North America, Latin America, Europe and the Asia-Pacific. Isolates were from patient infections (91.9% from blood cultures) collected during 1997-2008 and species identification was performed by at least two laboratories, including a reference laboratory (JMI Laboratories, North Liberty, Iowa, USA). Isolates were tested for serogroup identification by the University of Iowa Hygienic Laboratory (UHL; Coralville, Iowa, USA) using four antisera, including serogroups B or C or Y or W-135. Of the patients with a known age (51 out of 62 unique patients), 33 (64.7%) were under 30 years and 18 (35.3%) were over 30 with approximately equal numbers in each gender.

Isolates were tested using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution (M07-A8, 2009) methodology in cation-adjusted Mueller-Hinton broth (CA-MHB) panels supplemented with 2 to 5% lysed horse blood. Direct colony suspensions from a 20 to 24 hour growth plate from chocolate agar were used to obtain a 0.5 McFarland standard suspension. After inoculation, panels were incubated at 35ºC in 5% CO_2 for 20 to 24 hours. Numerous antimicrobial agents were tested including CEM-101, telithromycin, azithromycin, clarithromycin, erythromycin, penicillin, ceftriaxone, ciprofloxacin, levofloxacin, minocycline, rifampin and trimethoprim/sulfamethoxazole (TMP/SMX). Susceptibility to nalidixic acid was determined previously during routine testing as part of the SENTRY Antimicrobial Surveillance Program using dry-form broth microdilution panels (TREK Diagnostics, Cleveland, OH, USA).

Results

- All but two isolates were typeable using the four antisera available (Table 1). The majority of isolates were either serogroup B (37.1%) or C (40.3%) with smaller numbers of serogoups Y (16.1%) and W-135 (3.2%).
- Penicillin susceptibility was only 82.3%, with no resistant strains detected at a MIC value greater than 0.25 µg/ml (Table 2). All isolates were susceptible to ceftriaxone, azithromycin, minocycline and rifampin.
- Resistance to TMP/SMX was 59.7% and TMP/SMX -resistant strains were noted among all four serogroups (Table 2).
- Isolates were all susceptible to ciprofloxacin and levofloxacin with MIC values of ≤0.015 µg/ml (Table 2). However, 13 strains had reduced susceptibility to nalidixic acid (MIC, ≥8 µg/ml), which may correlate with diminished susceptibility to fluoroquinolones (CLSI M100-S19, 2009). Diminished fluoroquinolone activity was observed in strains from all four serogroups.
- CEM-101 had activity that was comparable to ceftriaxone and the fluoroquinolones which had MIC values of ≤0.015 µg/ml (Table 2).
- CEM-101 was the most active MLS_B agent tested (Table 3) with a MIC_{90} value of ≤0.015 µg/ml > telithromycin (0.03 µg/ml) > azithromycin and clarithromycin (0.12 µg/ml) > erythromycin (0.25 µg/ml).

Table 1. Distribution of serogroups among 62 isolates of *N. meningitidis* from the SENTRY Antimicrobial Surveillance Program (1997-2008).

Serogroup	Number (%)
B	23 (37.1)
C	25 (40.3)
Y	10 (16.1)
W-135	2 (3.2)
NT[a]	2 (3.2)

a. NT = Isolates were not typable using available antisera.

Table 2. Activity of CEM-101, macrolides, ketolides and other comparator agents tested against 62 isolates of *N. meningitidis*.

Antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% Susc.[a]	% Res.[a]
CEM-101	≤0.015	≤0.015	≤0.015-0.06	-[b]	-
Telithromycin	≤0.015	0.03	≤0.015-0.12	-	-
Azithromycin	0.06	0.12	≤0.015-0.12	100.0	-
Clarithromycin	0.03	0.12	≤0.015-0.25	-	-
Erythromycin	0.12	0.25	0.03-0.5	-	-
Penicillin	0.03	0.12	≤0.015-0.25	82.3	0.0
Ceftriaxone	≤0.015	≤0.015	≤0.015	100.0	-
Ciprofloxacin	≤0.008	≤0.008	≤0.008-0.015	100.0	0.0
Levofloxacin	≤0.008	≤0.008	≤0.008-0.015	100.0	0.0
Minocycline	0.12	0.12	≤0.008-0.25	100.0	-
Rifampin	0.015	0.06	≤0.008-0.12	100.0	0.0
TMP/SMX[c]	0.5	2	≤0.06-4	37.1	59.7

a. Susceptibility criteria based upon the CLSI (M100-S19, 2009).
b. Susceptibility criteria have not yet been proposed, but azithromycin at ≤2 µg/ml is considered susceptible.
c. Trimethoprim/sulfamethoxazole.

Table 3. MIC frequency distribution of CEM-101 compared to other MLS_B comparator agents tested against 62 *N. meningitidis* isolates.

Antimicrobial agent	Cumulative % of strains inhibited at each MIC (µg/ml) ≤0.015	0.03	0.06	0.12	0.25	0.5
CEM-101	**95.2**[a]	98.4	100.0	-	-	-
Telithromycin	58.1	**91.9**	98.4	100.0	-	-
Erythromycin	0.0	3.2	12.9	62.9	**98.4**	**100.0**
Clarithromycin	17.7	59.7	82.3	**98.4**	100.0	-
Azithromycin	3.2	40.3	88.7	**100.0**	-	-

a. Percent inhibited at MIC_{90} values are highlighted in bold for each agent.

Conclusions

- *N. meningitidis* that are serogroup B cause about one-third of all the meningococcus cases in the United States; in 2001, 65% of cases in infants (≤1 year of age) were caused by this serogroup. Unfortunately, no currently available vaccine protects against serogroup B. In this study, 37.1% of the *N. meningitidis* isolates tested were serogroup B and 69.2% of patients ≤ 5 years old were infected by this serogroup.
- *N. meningitidis* isolates with reduced susceptibility or resistance to β-lactams, fluoroquinolones and other classes of antimicrobial agents have been documented in countries worldwide.
- CEM-101 has potent activity (MIC_{90}, ≤0.015 µg/ml) against *N. meningitidis* isolates. This is 8- to 16-fold greater than commonly used macrolides.
- Pending additional studies, CEM-101 should be considered as a candidate to provide prophylaxis for the prevention and spread of *N. meningitidis* that may be resistant to currently prescribed anitimicrobial agents.

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