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Solithromycin (CEM-101) In vitro Susceptibility of *Bordetella pertussis*, an Emerging Respiratory Pathogen in the Adult

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Abstract

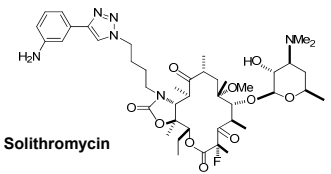
Background: Pertussis peaks every 3 to 5 years and more than 41,000 cases of pertussis were reported to CDC during 2012 and 18 pertussis-related deaths were noted by January, 2013. Although, the majority of deaths continue to occur among infants (< 3 months), and it is considered a disease of neonates and young children, increased rates of pertussis have been noted in adolescent children and adults. Other respiratory pathogens often cause clinical symptoms similar to pertussis and therefore many cases go unreported and outbreaks are difficult to manage. Since antibiotics are often administered in these respiratory infection outbreaks it is important that the antibiotic used provides adequate coverage for a broad range of potential pathogens. We have tested the in vitro activity of solithromycin (CEM-101), a new macrolide, the first fluoroketolide which is in Phase 3 clinical development for CABP, and comparator antibiotics.

Methods: 24 clinical strains of *B. pertussis* cultured from nasopharyngeal specimens collected in 2010-2013 were tested. MICs were determined by agar dilution methodology, as described by CLSI M7-A8, in Mueller-Hinton agar supplemented with 5% sheep blood. Organism suspensions harvested from fresh agar cultures were adjusted to yield a final test inoculum of 1 x 10^4 CFU/spot. Inoculated agar plates were incubated for 72 hours at 36° C in ambient air supplemented with 5% CO_2. MIC endpoints were read as the concentrations at which no growth, or a significant reduction of growth, was observed by visual inspection after incubation.

Results: The MIC90s and ranges for solithromycin and comparator drugs are shown in the Table.

	MICs (µg/ml)	
	MIC Range	MIC 90%
Solithromycin	≤0.002-0.03	0.015
Penicillin	1-2	2
Amoxicillin/Clavulanate	0.12-1	1
Cefdinir	8-16	16
Cefpodoxime	>32	>32
Azithromycin	0.03-0.12	0.12
Clarithromycin	≤0.015-0.06	0.06
Doxycycline	0.03-0.25	0.12
Trimethoprim / Sulfamethoxazole	1/19-4/76	4/76

Conclusion: The MIC of solithromycin for 100% of the twenty-four clinical strains of *B. pertussis* tested was ≤0.03 µg/ml and solithromycin was more active than older macrolides. Solithromycin, which has been shown to have broad coverage against other respiratory pathogens, may also be effective against *B. pertussis*.



Solithromycin

Introduction

Pertussis is a disease of neonates and young children but in recent years increasing cases of pertussis have been noted in young and older adults. The replacement of the old cellular pertussis component of DTP with the safer acellular vaccine has led to decreased immunity in populations (1). In California, 9000 cases of whooping cough were reported in 2012. This and other outbreaks clearly indicate that older children and adolescents need lasting immunity. Until a newer safe vaccine is developed, we are faced with treating pertussis in young adults and adults, as parents exposed to infected children also got pertussis. Pertussis in the adult is often difficult to recognize and appropriate treatment may not be administered. Older macrolides were safely used to cover a broad spectrum of respiratory pathogens. More recently, however, resistance to older macrolides has increased in respiratory pathogens. Solithromycin (CEM-101), a fourth generation macrolide and the first fluoroketolide, is currently in Phase 3 trials for moderate Community Acquired Bacterial Pneumonia (CABP). Solithromycin has been shown to be active against pneumococcus, *Moraxella catarrhalis*, *Haemophilus* spp., *Legionella* spp., *Chlamydophila, Mycoplasma pneumoniae*, MSSA and CA-MRSA among other CABP pathogens. Since pertussis in young and older adults could masquerade as CABP, we determined the minimum inhibitory concentrations (MICs) of solithromycin and comparator drugs for *Bordetella pertussis*.

Materials and Methods

Drugs. MICs of the following drugs were determined: amoxicillin/clavulanate (Sigma Lot# 100M0828v; USP, Lot# J0G109), azithromycin (USP, Lot# G; Sigma, Lot# E446421/1v), cefdinir (Sigma, Lot# 117K1392), cefixime (USP, Lot# F), cefpodoxime (USP, Lot# HDKD09), ceftriaxone (Sigma, Lot# 091M0741v), clarithromycin (USP, Lot# GIG324), clindamycin (Sigma, Lot# 021M1533v), daptomycin (Sigma, Lot# SLBD0350V), doxycycline (Sigma, Lot# BCBF9827V), levofloxacin (Sigma, Lot# BCBF7004V), linezolid (Sigma, Lot# 020M4707V), metronidazole (Sigma, Lot# 095K0693), penicillin (Sigma, Lot# BCBF3866V), CEM-101 (solithromycin) (Cempra, Lot# EKS11646), trimethroprim/sulfamethoxazole (Sigma, Lot# 000M4110V and BCBF0534v), vancomycin (Sigma, Lot# 120M1495V). Drugs were dissolved and diluted for testing per recommendations in CLSI M100-S22 (2).

Organisms. Clinical strains were cultured from patient specimens submitted to the Clinical Microbiology Laboratories at the University of Rochester Medical Center, Rochester, NY. MICs of solithromycin and comparator drugs were determined for twenty-four clinical strains of *B. pertussis* cultured from nasopharyngeal specimens collected in 2010-2013.

MIC Determinations. Prior to testing, *B. pertussis* was subcultured onto Mueller-Hinton Agar supplemented with 5% sheep blood for 48 hours at 36° C in ambient air supplemented with 5% CO_2. MICs of solithromycin and comparator drugs for *B. pertussis* were determined by agar dilution methodology in Mueller-Hinton agar supplemented with 5% sheep blood as described by CLSI M7-A8 (3). Organism suspensions harvested from fresh agar cultures were adjusted to yield a final test inoculum of 1 x 10^4 CFU/spot. Inoculated agar plates were incubated for 72 hours at 36° C in ambient air supplemented with 5% CO_2.

The MIC endpoints for drugs were read as the concentrations at which no growth, or a significant reduction of growth, was observed by visual inspection after incubation.

The performance of test reagents (including drug potency) and equipment, and test personnel was monitored using aerobic quality control organisms as recommended by CLSI (2). MICs of all drugs for quality control organisms tested in parallel with test organisms were within acceptable ranges as recommended by CLSI.

Results

MICs of solithromycin and comparator drugs for 24 clinical strains of *B. pertussis* were determined. The frequency distributions of MICs of each drug for all strains tested are presented in Table 1. The range of MICs, MICs for 50% of strains and MICs for 90% of strains for all drugs are presented in Table 2.

Table 1. MIC Distributions against 24 clinical strains of *B. pertussis*

Drugs	No. of occurrences at MIC (µg/mL) of:															
	≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Solithromycin	2	3		18	1											
Penicillin										4	20					
Amoxicillin / Clavulanate							3			21						
Cefdinir													2	22		
Cefpodoxime																24
Azithromycin					6	2	16									
Clarithromycin				3	4	17										
Doxycycline					5	3	14	2								
Trimethoprim / Sulfamethoxazole									1	20	3					

Table 2. Activity Against *B. pertussis*

Drugs	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Solithromycin	≤0.002-0.03	0.015	0.015
Penicillin	1-2	2	2
Amoxicillin / Clavulanate	0.12-1	1	1
Cefdinir	8-16	16	16
Cefpodoxime	>32	>32	>32
Azithromycin	0.03-0.12	0.12	0.12
Clarithromycin	≤0.015-0.06	0.06	0.06
Doxycycline	0.03-0.25	0.12	0.12
Trimethoprim / Sulfamethoxazole	1/19-4/76	2/38	4/76

Conclusions

The MIC of solithromycin for 100% of the twenty-four clinical strains of *B. pertussis* tested was ≤0.03 µg/ml. Solithromycin was more active than azithromycin and clarithromycin against *B. pertussis*. Solithromycin is active against a broad spectrum of respiratory pathogens and is being tested as monotherapy in moderate to moderately severe CABP Phase 3 trials. The results from this study shows that solithromycin could provide coverage against pertussis.

References

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3. Clinical and Laboratory Standards Institute. Methods for Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Eighth Edition. CLSI document M7-A8.