

Efficacy of a Next Generation Fluoroketolide, Solithromycin (CEM-101), for Experimental Otitis Media (EOM) due to either Nontypeable *Haemophilus influenzae* (NTHi) and *Streptococcus pneumoniae* (SP)

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Background: Solithromycin is a next-generation fluoroketolide with in-vitro antibacterial activity against multidrug-resistant SP, including erythromycin resistant (ER) isolates and both β -lactamase positive and negative NTHi.

Methods: Plasma PK parameters (C_{max} and AUC_{0-24}) and MEF concentrations were determined on day 1 and 3 after administration of 150 mg/kg once per day of Solithromycin via gavage. Isolates with specified antimicrobial susceptibility patterns were inoculated directly into the middle ear (ME). Plasma and MEF were collected for Solithromycin PK studies and MEF cultures performed to determine efficacy.

Results: Solithromycin administered at 150 mg/kg/day resulted in the following PK parameters: C_{max} and AUC_{0-24} were 2.2 μ g/ml and 27.4 μ g.h/ml in plasma and 1.7 μ g/ml and 28.2 μ g.h/ml, in extracellular MEF on day 1. By day 3, C_{max} and AUC_{0-24} had increased to 4.5 μ g/ml and 54 μ g.h/ml in plasma and 4.8 μ g/ml and 98.6 μ g.h/ml in extracellular MEF, respectively. For NTHi EOM, 3 isolates with MIC/MBC [BCH1:0.5/1; 1247: 2/2 and 1213: 4/4 μ g/ μ l] were selected for study. On day 3 of therapy, Solithromycin at 150 mg/kg/day sterilized the middle ear fluid in > 85% of animals infected with BCH1 (MIC= 0.5 μ g/ml) and 1247 (MIC=2 μ g/ml). For NTHi 1213, > 85% of MEF cultures remained positive on day 3 of therapy. Solithromycin sterilized the MEF in 100% of animals infected with SP 331 (MIC= 0.06 μ g/ml) and SP CP-645 (MLSB phenotype; MIC 0.125 μ g/ml). Middle ear infection persisted in 60% of animals infected with CP-712 (M phenotype; MIC=0.5 μ g/ml).

Conclusion: In chinchilla model of EOM, Solithromycin at 150 mg/kg/day for 3 days sterilized MEF in >85% animals challenged with NTHi isolates with $MIC \leq 2 \mu$ g/ml. For EOM due to SP; Solithromycin at 150 mg/kg/day sterilized EOM due to SP with $MIC \leq 0.125 \mu$ g/ml. Solithromycin activity against both NTHi and SP suggest further evaluation for treatment of respiratory tract infection, including acute otitis media, is warranted.