Inhibition of Protein Synthesis and Ribosome Biogenesis in *Staphylococcus aureus*, *Haemophilus influenzae* and *Streptococcus pneumoniae* by solithromycin, a new fluoroketolide.

**For Publication**

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**Objectives.** The continuing increase in antibiotic resistant microorganisms is driving a search for improved antimicrobial agents. Ketolides are third generation semi-synthetic derivatives of macrolide antibiotics. Solithromycin (CEM-101) is a novel fluoroketolide with improved antimicrobial effectiveness. This compound, like other macrolides, binds to the 50S subunit of the bacterial ribosome and inhibits protein biosynthesis. It binds to domains II and V of 23S rRNA and its 2-fluoro group associates with the floor of the peptide tunnel. Like other ketolides, it should impair ribosomal subunit formation. This mechanism of action was examined in strains of *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*.

**Methods.** For each organism, IC\(_{50}\) values were determined for the inhibitory effects of solithromycin on cell growth rates and viability by cfu determinations. Protein synthesis was measured by \(^{35}\)S-methionine incorporation into cellular proteins. Ribosomal subunit synthesis rates were assayed by \(^{3}\)H-uridine labeling of RNA in cells followed by ribosomal subunit separation using sucrose gradient centrifugation. RNA turnover was assayed by a gel on a chip procedure.

**Results.** The mean IC\(_{50}\) values for solithromycin inhibition of cell viability, protein synthesis and growth rates were 7.5 ng/mL for *S. pneumoniae*, 40 ng/mL for *S. aureus* and 125 ng/mL for *H. influenzae*. Net 50S subunit formation was reduced in all three organisms with IC\(_{50}\) values similar to those above. Solithromycin showed IC\(_{50}\) values comparable to telithromycin in *S. pneumoniae* and *S. aureus* but the IC\(_{50}\) value was 10-fold less than that of telithromycin in *H. influenzae*. The rates of 50S synthesis were diminished by 2 to 5-fold at the IC\(_{50}\) concentration. Turnover of 23S rRNA was stimulated by this ketolide as seen previously with telithromycin.

**Conclusion.** Solithromycin was found to be a particularly effective antimicrobial agent with IC\(_{50}\) values comparable to the ketolide telithromycin and was significantly more effective than azithromycin and clarithromycin against these three microorganisms.