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**Antimicrobial Characterization of CEM-101: PAE, Bactericidal Activity and Combinations**

**HS SADER, DJ BIEDENBACH, PR RHOMBERG, RN JONES**

**JMI Laboratories, North Liberty, Iowa**

**ABSTRACT**

CEM-101, a novel macrolide-ketolide class antibiotic, is being developed for the oral treatment of community-acquired respiratory tract infections (CA-RTI) and uncomplicated skin and skin-structure infections (USSSI). The high potency of CEM-101 against Streptococcus pneumoniae, S. pyogenes (β-haemolytic and viridans group streptococci), Staphylococcus epidermidis and coagulase-negative staphylococci has been documented in early screening studies performed using reference Clinical and Laboratory Standards Institute (CLSI) methods.

Background: CEM-101, a new macrolide-ketolide for respiratory tract infection therapy, was tested to determine its killing activity and killing curves (PAE) by checkerboard on 20 strains (7 groups). PAE was tested at 5X concentration for 1 or 2 hours exposure. TEL was used as control. Daily bacterial emergence was performed by checkerboard on 20 strains (8 groups). PAE was tested at 2X, 4X, 8X MIC and colony counts were performed at T1, T2, T4, T8 and T24.

The tested Gram-positive and -negative pathogens were as follows: S. pyogenes strains (Table 3). CEM-101 produced a greater reduction of CFU/mL and more rapid killing when compared to either tetracycline or the macrolides clarithromycin and azithromycin.

**RESULTS**

- After two hours of exposure, the PAE of CEM-101 (2X concentration) was similar to tetracycline (2.3 hours) when tested against S. aureus at 4X MIC value. By increasing the concentration during the exposure to 8X the MIC, the PAE of CEM-101 was extended to 3.9 hours in all strains studied.

- CEM-101 PAE tested against S. aureus and S. pyogenes was 3.0 and 6.1 hours compared to 1.9 and 2.4 hours, respectively for tetracycline. CEM-101 PAE against Gram-negative pathogens (Table 1) also showed the new agent versus the old antibiotics.

- In general, CEM-101 exhibited MIC/MIC ratios of 4 (bactericidal activity) when tested against macrolide-susceptible streptococci and CoNS. In contrast, S. aureus and enterococci had some elevated MBC values (Table 2).

- CEM-101 showed rapid bactericidal activity reduction of 33 log10 CFU/mL against macrolide-susceptible strains of S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes (only at 8X MIC) and viridans group streptococci (Table 3). CEM-101 produced a greater reduction of CFU/mL and more rapid killing when compared to either tetracycline or the macrolides clarithromycin and azithromycin.

- The most common interaction category observed for the CEM-101 drug combination studies was indifference (16 occurrences), followed by additive (22), and partial synergy (7) effects. Synergy was only observed CEM-101 and gentamicin for S. pneumoniae (paucity of data).

**MATERIALS AND METHODS**

PAE testing: MIC values for CEM-101 and tetracycline were determined using established protocols and methods. CEM-101 was combined with tetracycline in a checkerboard format. CEM-101 was combined with five other antimicrobials against 6 ß-haemolytic streptococci and 7 S. aureus strains (see Table 3) according to methods described by Moody et al. (2004).

**CONCLUSIONS**

- CEM-101 showed a significant concentration and exposure-dependent PAE against Gram-positive (average PAE, 3.8 hours) and Gram-negative (average PAE, 4.0 hours) pathogens in combination with CoNS and pneumococcus, and showed significant synergy with S. pneumoniae. CEM-101 MIC/MIC ratios can be high for S. aureus, but some strains showed MBC results that were similar to the reference agents.

- CEM-101 exhibited bactericidal activity when tested against macrolide-susceptible streptococci, CoNS and macrolide-resistant dendritic pathogens such as S. pneumoniae. CEM-101 MIC/MIC ratios can be high for S. aureus, but some strains showed MBC results that were similar to the reference agents.

**SELECTED REFERENCES**