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WCK 4873 (Nafithromycin): Impact of hyper ermB induction in S. pneumoniae and S. aureus on the activity of ketolides

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Background: *ermB* (Erythromycin Ribosome Methylase) gene is responsible for causing mono-/di methylation of A2058 residue in domain V of 23S rRNA thus impacting the target affinity of macrolides, clindamycin and even to a varying extent for ketolides. However, ketolides possess the unique feature of activity against macrolide-resistant *ermB*-expressing *S. pneumoniae* (SPN) and *S. pyogenes* (SPY) and are non-inducers of this enzyme which is not the case with 14 and 15 membered macrolides. However, for older ketolides, a lower potency has been reported against high-level *ermB* strain mostly due to suboptimal target affinity. We compared the potency of newer ketolides, against *ermB* strains with varying level of induction employing erythromycin (ERY) as an inducer. WCK 4873 is a novel lactone ketolide active against typical and atypical respiratory pathogens including macrolide-resistant SPN and SPY and has completed Phase 1 studies in Europe. In this study, we describe the activity of WCK 4873 and other ketolides under hyper-induction state of *ermB* in SPN and *S. aureus* (SA).

Material/methods: *ermB* induction was undertaken by determining the MICs in presence of ERY (1 µg/mL). Moreover, for attaining even high-level of induction, the MICs of newer ketolides were determined in the presence of ERY using overnight pre-induced (ERY 5 µg/mL) cultures. MICs were determined by agar dilution method employing 15 macrolide-resistant strains each of SPN (ERY MIC_{90} - >32 µg/mL) and SA (ERY MIC_{90} - >32 µg/mL) using Mueller-Hinton agar supplemented with or without 5% sheep blood.

Results: WCK 4873 showed lowest MICs against un-induced *ermB* SPN isolates with $MIC_{50/90}$ as 0.03/0.12 µg/mL. MIC_{90} of WCK 4873 and Telithromycin (TEL, MIC_{90}: 0.5 µg/mL) did not change in ERY supplemented medium. However, for Cethromycin (CET), the MIC_{90} under induced condition rose from 0.5 to 4 µg/mL. Under hyper-induction conditions employing both ERY exposed overnight inoculum as well as MICs in ERY supplemented medium, the MIC_{90}s of TEL, CET and Solithromycin

(SOL) were 1, 4 and 4 µg/mL, respectively while WCK 4873 MIC_{90} shifted by just one-dilution to 0.25 µg/mL. For SA the $MIC_{50/90}$ (µg/mL) determined in absence and presence of ERY were: WCK 4873 – 0.12/0.25 and 4/>32, TEL – 0.25/2 and 8/>32, CET – 0.12/0.5 and 4/>32 and SOL – 0.12/0.5 and 8/>32 respectively.

Conclusions: Among the ketolides studied, WCK 4873 (Nafithromycin) showed the least impact of *ermB* mediated hyper di-methylation in SPN and SA indicating higher affinity towards hyper methylated ribosomes.