Activity of a novel ketolide A against haemophilus influenzae using in vitro and in vivo pharmacodynamic models

M. Pandya1, M. Rao2, T.K. Barmana2, R. Sood2, S. Dube2, R. Venkataramanan3,*
1 Daiichi Sankyo India Pharma Private Limited, Gurgaon, India
2 Daiichi Sankyo India Pharma Private Limited, Gurgaon, Haryana, India
3 Daiichi Sankyo India Pharma Private Limited, Gurgaon, India

Background: Haemophilus influenzae causes community-acquired respiratory tract and invasive infections in humans. Resistance to macrolides and fluoroquinolones is emerging in H. influenzae limiting its therapeutic options. In the present study we demonstrated in vitro and in vivo potential of this novel ketolide against H. influenzae.

Methods & Materials: MIC of fresh clinical isolates of H. influenzae (n=145) (β-lactamase producer, non-producer strains and standard ATCC quality control strains) from tertiary care centers in India was evaluated using microbroth dilution method (CLSI). Bactericidal potential was evaluated using time kill kinetics method against 3 strains. Immunocompromised mouse and rat pneumonia model were performed against 2 clinical isolates of H. influenzae. Plasma and ELF concentrations were estimated using standard HPLC analysis and Microbiological method.

Results: Ketolide A showed MIC range of 0.03 - 4 μg/ml against fresh clinical isolates of H. influenzae. Ketolide A was bactericidal against 3 different strains of H. influenzae at 4X MIC concentration and the results were comparable with telithromycin. Ketolide A showed >1 log10 reduction in the CFU/lungs compared to 2 h control at 100 mg/kg BW PO bid in rat and mouse immunocompromised pulmonary infection models. The efficacy of ketolide A correlated with its accumulation in rat lung tissue much above its MIC levels (1-2 μg/ml) up to 8h.

Conclusion: Efficacy of ketolide A in rodent H. influenzae models and high concentration in ELF and lung tissue warrants its further investigation for the treatment of H. influenzae infections.

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