Rx-P873, a novel protein synthesis inhibitor, accumulates in human THP-1 monocytes and is active against extracellular and intracellular Pseudomonas aeruginosa (Pa).

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Abstract (revised)

Background: Pseudomonas aeruginosa is an opportunistic pathogen responsible for severe pulmonary infections in debilitated patients hospitalized in ICU or suffering from cystic fibrosis. Infections caused by Pa aeruginosa are difficult to treat due to (i) the remarkable ability of the pathogen to express constitutive and inducible resistance mechanisms (low permeability of the outer membrane, efflux pumps overexpression, enzymatic inactivation of antibiotics) and (ii) its ability to enter and survive in eucaryotic cells, where the efficacy of antibiotics is considerably reduced [1].

Results: RX-P873 accumulates ~6-8 fold in THP-1 cells, with concentrations ranging from 1000 to 10,000 CFU/mL; plating and CFU counting after infections. We explored novel antibacterial agents acting on unexploited targets is critically needed to cope with infections caused by multiresistant organisms [2]. Exploring their cellular pharmacokinetics and pharmacodynamics may help to correctly position them for the treatment of persistent or recurrent infections where intracellular survival may play an important role.

Methods: Extracellular and intracellular activities against sensitive and MDR Pa strains isolated from cystic fibrosis. Concentration in cells was assayed by fluorimetry (λexc = 450nm). Cellular concentration calculated using as reference the sample protein content. MICs were measured by microdilution (CLSI). Extracellular and intracellular activities were assayed using a PD model (AAC 5723104) for determination of apparent static concentrations (Cs) and relative activities at 20 mg/L, or at 50% MIC (Cs/EMIC). Concentration in cells was assayed by fluorimetry (λexc = 280nm, λem = 450nm).

Conclusions: RX-P873 shows similar MIC against a fully susceptible and a MDR strain as well as against a series of SCVs.

References


Aims of the study

• to determine the cellular accumulation of RX-P873 in THP-1 human monocytes
• to compare its extracellular and intracellular activity with that of ciprofloxacin and cefazidime against susceptible and MDR Pa aeruginosa using a pharmacodynamic model recently developed in our laboratory [1].

Method

SUSCEPTIBILITY TESTING: RX-P873 shows similar MIC against a fully susceptible and a MDR strain as well as against a series of SCVs.

Acknowledgements

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