Efficacy of Inhaled Amikacin and Fosfomycin in a Rat Model of Acute Pseudomonas-Induced Pneumonia

charles river

M. C. McElroy[1#], A. T. Marsden[1], S. K. Gandi[1], P. Smith[2], X. Li[2], S. Beck[3], A. Montgomery[3]

[1] Respiratory Pharmacology, Charles River, Edinburgh, United Kingdom,
[2] Inhalation Toxicology, Charles River, Edinburgh, United Kingdom, [3] Avalyn Pharma, Seattle, WA, United States.

[#] Corresponding author: Mary.McElroy@crl.com

1 Introduction

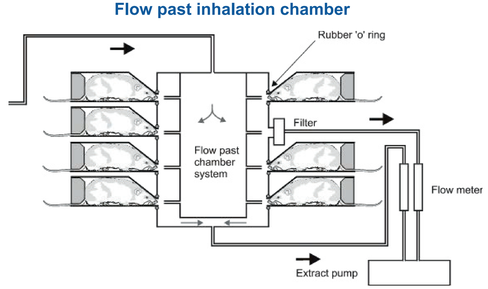
Pseudomonas aeruginosa is a major cause of ventilator acquired pneumonia (VAP) and a risk factor for Adult Respiratory Distress Syndrome (ARDS). Rapid treatment of infection after diagnosis is important to prevent mortalities and the inhaled route of delivery targets the lung parenchyma while limiting systemic exposure. The objective of this study was to determine whether inhalation of the combination antibiotic formulation (Amikacin:Fosfomycin [AFA] at ratio of 5:2 mg basis) reduced clinical signs and the number of viable bacteria (CFUs) in a rat model of Pseudomonas induced pneumonia.

2 Methods

Male SD rats (n = 5 per group) were administered a clinical strain of *Pseudomonas aeruginosa* (MIC, Minimum Inhibitory Concentration > 32 mg/L for Amikacin) directly to the lungs by oropharyngeal aspiration (T = 0 hrs); animals where monitored for 6 hrs. Body temperatures were recorded every 30 mins and CFUs were determined at the end of the study. Animals were exposed to inhaled antibiotic in a flow past inhalation chamber at 1 hrs post administration of pseudomonas. Test aerosol concentrations were determined by chemical analysis and a Marple Cascade impactor was used to determine the Mass Median Aerodynamic Diameter (MMAD) of test aerosol. Pseudomonas/Vehicle controls were exposed to vehicle alone (MilliQ water). Data presented as Mean ± S.D. Statistical comparisons were performed against Vehicle Control using ANOVA with Dunnett's post test analysis. *p≤0.05, **p≤0.01, ***p≤0.001, ****p≤0.0001

3 Results

Flow past inhalation chamber



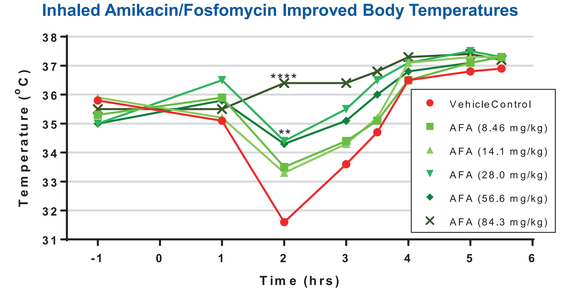
The flow past inhalation chamber is a nose-only inhalation exposure chamber in which fresh aerosol is flowed past each exposure port and exhaled air is immediately exhausted. This allows all animals in the chamber to be exposed to the same aerosol concentration. (McDonald K. E. *et. al.,* 2010)

Delivered Aerosol Dose of Amikacin/Fosfomycin

Treatment	Innocula Dose (CFU/Lung)	Exposure duration (mins)	Estimated Delivered Dose Combined Amikacin/Fosfomycin (mg/kg)
P. aeruginosa + Vehicle	10^6	60	0
P. aeruginosa + Amikacin/Fosfomycin	10^6	6	8.46
		10	14.1
		20	28.0
		40	56.6
		60	84.3

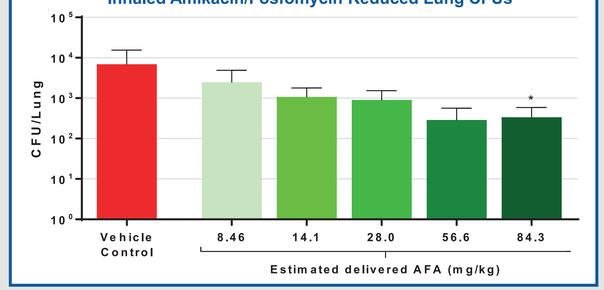
Estimated delivered inhalation doses ranged between 8.46 mg/kg to 84.3 mg/kg (total antibiotic administered) and test aerosols were respirable to rats (i.e. MMAD 2.35 µm for amikacin and 3.16 µm for fosfomycin).

Inhaled Amikacin/Fosfomycin Improved Body Temperatures



Group mean body temperatures were reduced in Pseudomonas/Vehicle controls at 2 hrs post dose compared with pretrial values. However, inhaled antibiotic prevented this reduction in body temperature in a dose-dependent manner.

Inhaled Amikacin/Fosfomycin Reduced Lung CFUs



Group mean lungs CFUs were also reduced in a dose-dependent manner in antibiotic treated animals in comparison with the Pseudomonas/Vehicle.
The administration of vehicle (MilliQ Water) did not effect Pseudomonas-induced changes in body temperatures or final lung CFUs.

Pseudomonas + Vehicle group Pseudomonas + (Amikacin/Fosfomycin) groups

4 Conclusion

Administration of inhaled combination antibiotic treatment (Amikacin/Fosfomycin,84.3 mg/kg, 5:2 ratio) significantly reduced lung CFUs and improved body temperatures in a rat model of acute pneumonia caused by a clinical strain of Pseudomonas. These data demonstrate that inhaled antibiotics may have therapeutic benefit for ventilator acquired pneumonia.