ATS C22 - Efficacy Of Fluticasone And Salmeterol In A Novel Inhaled Dry Powder Delivery Platform


RATIONALE: The efficient delivery of therapeutics at high doses to the airways and lung in dry powder (DP) form remains a challenge. We are developing a salt-based DP platform using small diameter particles that are dispersible in a flow rate independent manner. A primary benefit of the technology is the ability to deliver larger drug payloads than many conventional DP technologies. The aim of this study was to determine the efficacy of a proof-of-concept DP formulation comprised of the corticosteroid, fluticasone propionate (FP, 13.5% w/w), and a long acting bronchodilator, salmeterol xinafoate (SX, 2.0% w/w), in a rodent model of LPS induced, acute lung injury.

METHODS: Airway Hyperreactivity: Female Balb/c mice (19-21g) were exposed to 20 minutes of 0.5 mg/ml nebulized lipopolysaccharide (LPS, Pseudomonas aeruginosa) 24 hours prior to specific airway resistance measurements (sRaw). sRaw was determined by dual chamber plethysmography (EMKA technologies, VA). Baseline measurements (5 minutes) were collected prior to treatment with aerosolized DP FP/SX or placebo (leucine) DP. Following treatment animals were returned to the plethysmograph and another 5 minutes of measurements were taken prior to escalating doses of aerosolized methacholine (MCh) delivered in the head chamber (0, 6.25, 12.5 mg/ml). Inflammation: Mice were treated with aerosolized FP/SX or leucine control DP 1 hour prior to LPS administration. The mice received 0.3µg of LPS intranasally in 50µl isotonic saline for inhalation, and 4 hours post LPS administration broncho-alveolar lavage (BAL) was performed for inflammatory cell counts.

RESULTS: FP/SX dry powder treatment resulted in a decrease in sRaw from untreated baseline measurements (-27% of baseline). The FP/SX treatment also reduced sRaw (-39%) compared to post-treatment levels leucine treated control animals. Similarly, FP/SX treatment reduced sRaw over the duration of MCh challenge, with a sRaw reduction of 33%. Additionally, treatment with FP/SX in LPS challenged mice resulted in a significant decrease in total inflammatory cells in the BAL with respect to leucine control (1.11x10^6 vs. 5.00x10^5, p<0.001), primarily a result of reduced neutrophil accumulation.

CONCLUSIONS: Aerosol delivery of FP/SX in a novel DP delivery platform reduced both inflammation and airway hyperreactivity in a mouse model of acute lung injury. These data suggest that the technology may be a suitable platform for pulmonary drug delivery and provide a framework for future work involving the delivery of high drug loads to the airways and/or lung for a wide range of respiratory conditions.