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Title: Pharmacokinetics of tobramycin nebulizer solution (300mg/4ml) administered by Pari e-Flow rapid vs Pari LC plus nebulizer in patients with cystic fibrosis and Pseudomonas aeruginosa infection

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Body: Background: New generation nebulizers are increasingly used to reduce the time required for inhalation, potentially improving patient compliance. Objectives: To compare the pharmacokinetic (PK) profile of tobramycin nebulizer solution (TNS) 300mg/4mL (Bramitob®) administered with the Pari e-Flow rapid versus the Pari LC plus nebulizer. Methods: Randomized, crossover trial, enrolling 27 cystic fibrosis (CF) patients with chronic Pseudomonas aeruginosa infection. Patients received two twice-daily, 28-day treatment periods with TNS 300mg/4mL delivered by either nebulizer, separated by a 4-week wash-out. Blood and sputum samples were collected on days 1 and 28 over the first 12 and 8 hours, respectively. Primary endpoints were plasma tobramycin maximum concentration (C_{max}) and area under the curve (AUC_{0-t}) on day 28. Results: 27 patients were randomized and 25 completed the study. Patients were 18-47 (mean 25.5) years old. On Day 28, the geometric mean ratios (e-Flow rapid:LC Plus) for plasma tobramycin C_{max} and AUC_{0-t} were 0.85 (90% CI 0.61-1.19) and 0.87 (90% CI 0.65-1.18), respectively, while the geometric mean ratios for sputum tobramycin C_{max} and AUC_{0-t} were 1.40 (90% CI 0.86-2.27) and 1.37 (90% CI 0.80-2.33), respectively. Nebulization time was significantly shorter for the eFlow rapid as compared to the LC plus: 5.7±2.0 versus 12.1±2.2 min (mean ± SD on day 28). Conclusion: Plasma and sputum PK data support comparable pulmonary delivery of TNS 300 mg/4mL in CF patients using different nebulizers with a shorter nebulization time for the Pari e-Flow device. Supported by: Chiesi Farmaceutici.