Abstract

Background: Combihaler could connect both pressurized metered dose inhalers (pMDIs) and nebulizers to non-invasive ventilation (NIV) circuit. This can be used to give the patient a preliminary bronchodilator dose in an attempt to increase forced expiratory volume in one second pre-nebulization.

Aim of the work was to study the effectiveness of combihaler in salbutamol delivery with and without a preliminary bronchodilator dose compared with aerogen standard adult t-piece in single-limb NIV.

Methods: *In-Vitro*: Two milliliters of salbutamol solution (10000 μg) were nebulized using aerogen solo nebulizer (SOLO) with three connection setting; I: t-piece, II: combihaler and III: combihaler with pMDI. Only with connection III, two pMDI doses, containing 100 μg salbutamol each, were actuated pre-nebulization. Fate of nebulized dose was determined together with aerodynamic characteristics by anderson cascade impactor. *In-vivo* and *Ex-vivo*: Twelve NIV chronic obstructive pulmonary disease patients were included in six days urinary pharmacokinetic study in which 1 ml salbutamol solution (5000 μg) was nebulized using SOLO with the three connection settings randomized in days 1, 3 and 5 of the study. Only with connection III, the preliminary bronchodilator dose (200 μg salbutamol through pMDI) was given pre-nebulization. Urine samples were collected 30 min and pooled for 24 hr post-dose and extracted through solid phase extraction. At days 2, 4 and 6; *ex-vivo* study was carried out. All samples were analyzed using high performance liquid chromatography.

Results: No significant difference was found *in-vitro* in the fate of nebulized dose between the three connections. However, combihaler with pMDI had significantly

greater fine particle dose less than or equal 5 μm as percentage of nominal dose and mass median aerodynamic diameter than both t-piece and combihaler without pMDI. However, t-piece had significantly higher fine particle fraction less than or equal 3 μm than both combihaler connections (II and III). No significant difference was found between the three connections for *in-vivo* and *ex-vivo* results which showed that combihaler with pMDI achieved the highest salbutamol fractions on both *ex-vivo* filters and lung bioavailability (urinary salbutamol 30 min post-dose). However, t-piece had the lowest body bioavailability (urinary salbutamol 24 hr post-dose).

Conclusion: T-piece and combihaler are equally efficient for salbutamol delivery from SOLO in single-limb NIV. However adding a preliminary bronchodilator dose pre-nebulization was found to alter aerodynamic characteristics to a significant level and optimizes the inhaled salbutamol fraction delivered to lungs to a statistically non-significant level.

Keys words: Salbutamol; NIV; COPD; SOLO; Combihaler; T-piece; pMDI; Preliminary bronchodilator dose; Lung; bioavailability.