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Lung deposition and systemic bioavailability of different aerosol devices with and without humidification in mechanically ventilated patients

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ABSTRACT

Background: During mechanical ventilation medical aerosol delivery has been reported to be upto two fold greater with dry inhaled gas than with heated humidity. Urine levels at 0.5 h post dose (URSAL0.5%) has been confirmed as an index of lung deposition and 24 h (URSAL24%) as index of systemic absorption. Our aim was to determine the effect of humidification and aerosol device type on drug delivery to ventilated patients using urine levels.

Methods: In a randomized crossover design, 36 (18female) mechanically ventilated patients were assigned to one of three groups. Groups 1 and 2 received 5000 μg salbutamol using vibrating mesh (VM) and jet nebulizers (JN), respectively, while group 3 received 1600 μg (16 puffs) of salbutamol via metered dose inhaler with AeroChamber Vent (MDI-AV). All devices were placed in the inspiratory limb of ventilator downstream from the humidifier. Each subject received aerosol with and without humidity at >24 h intervals with >12 h washout periods between salbutamol doses. Patients voided urine 15 min before each study dose and urine samples were collected at 0.5 h post dosing and pooled for the next 24 h.

Results: The MDI-AV and VM resulted in a higher percentage of urinary salbutamol levels compared to the JN ($p < 0.05$). Urine levels were similar between humidity and dry conditions.

Conclusions: Our findings suggest that in-vitro reports overestimate the impact of dry vs. heated humidified conditions on the delivery of aerosol during invasive mechanical ventilation.

Introduction

Inhaled aerosol delivery during conventional mechanical ventilation with dual limb circuits, has been reported to be 40–80% greater with dry ambient inhaled gas than with heated humidity.[1–3] For this reason, it has been suggested that clinicians should turn off the humidifier before starting aerosol delivery. Studies have shown that there is no significant difference between aerosol delivery in dry and humidified conditions in a single limb non-invasive ventilation (NIV) bench model study[4] and in automatic continuous positive airway pressure (Auto-CPAP) by patients' study.[5] However, this data cannot be extended to dual limb ventilation because of difference in aerosol generator positioning.

Location of study: Teaching Hospital of Faculty of Medicine, Faculty of Medicine, Beni-suef University, Beni-suef, Egypt and the Clinical Pharmacy Department, Faculty of Pharmacy, Beni-suef University, Beni-suef, Egypt (analysis).

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The debate of potential benefit of turning off the humidifier while delivering aerosol was addressed by Lin et al., reporting that turning off the humidifier for 20 min before aerosol delivery with MDI did not increase inhaled dose delivered to the ventilated patient. They attributed this to presence of condensate in the circuit that kept absolute humidity high despite reduced circuit temperature.[6] More recently, Ari et al. demonstrated that in-vitro models simulating active exhaled humidity, more closely represent actual patient airway interactions, reducing differences in aerosol delivery between dry and humidified ventilator circuit, suggesting that models using passive or dry exhalation may overestimate total inhalable dose (TID) under dry conditions.[7] Consequently, reports of better TID from aerosol delivered with dry versus heated humidified conditions might be due to failure of the models to simulate exhaled heat and humidity.[7] The debate was furthered with reports of no difference of patients' clinical status with changing humidity during aerosol delivery to ventilated patients.[8] This suggests that a more reliable method is needed to determine the effect of humidity on aerosol delivery in the ventilated patient.

Urine drug levels of salbutamol have been correlated to pulmonary delivery efficiency of inhaled medication.[9,10] It has been previously shown that urinary salbutamol levels at 0.5 h post administration and cumulative over 24 h can be used as indices of the pulmonary deposition and systemic absorption of inhaled medication.[9,10] The urinary drug level post aerosol administration has been used with other inhaled medications e.g. Sodium cromoglycate,[11] Formatrol,[12] Terbutaline,[13] Tobramycin.[14] The non-invasive urinary pharmacokinetic method has been used to compare delivery of a broad range of aerosol devices and administration methods: metered dose inhalers (MDI) to MDI with spacers[15,16]; investigate optimum inhalation technique[17]; compare dry powder inhalers (DPI) to MDIs[18]; determine the relative bioavailability of nebulized drug with prolonged administration[19,20]; and compare the use of highly resistant DPI in normal subjects to chronic obstructive lung disease (COPD) patients.[21] In addition, urine levels have been used to study lung deposition and systemic absorption in critically ill patients e.g. during and following exacerbations.[22,23] and during mechanical ventilation.[24–27]

Multiple data mining modelling studies have correlated urinary salbutamol method to in-vitro aerosol inhaled dose data.[25,27,28] including mechanically ventilated patients.[25,27] demonstrating that urinary salbutamol excreted at 0.5 h post dosing correlated to the fine particle dose (FPD) inhaled, and the mass median aerodynamic diameters (MMAD). They also showed that the urinary salbutamol excreted cumulatively collected over 24 h post dosing correlates to the total inhalable dose that reaches the patient. Consequently, urinary salbutamol method was proven to be a reliable method that can provide indices of lung deposition and systemic absorption.

The aim of the present study was to determine the effect of humidification and type of inhalation device on aerosol delivery using salbutamol urine levels as indices of lung deposition and systemic absorption in mechanically ventilated patients.

Materials and methods

Study population

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review board (IRB) and independent ethics committees approved the protocol, with written informed consent obtained from all subjects. All subjects were recruited using hospital approved delayed consent procedure.

Inclusion criteria was for subjects with a previous diagnosis of asthma or bronchospastic COPD that were admitted to the respiratory unit with an acute exacerbation, receiving invasive ventilation and prescribed to receive aerosol salbutamol. Subjects were excluded if they had taken part in a research study during the previous 6 months, had known hypersensitivity to salbutamol, systolic blood pressure of <100 mmHg or severe renal impairment defined as Creatinine Clearance or eGFR of <20 mL min^{-1}.

Study design and procedures

We used the urinary salbutamol methodology previously reported by Hindle et al.[9] to associate inhaled aerosol dose and urine levels of drug due to systemic absorption comparing three aerosol delivery methods during mechanical ventilation with and without heated humidification.

In a randomized crossover design, asthmatic subjects receiving volume assisted control (V/AC) invasive mechanical ventilation using Bellavista 1000e Ventilator (Imtmedical, Buchs, Switzerland) and Ultramed endotracheal tube (cuffed) size 8 (Ultra For Medical Products Co., Cairo, Egypt) were randomly assigned to receive aerosol with a vibrating mesh nebulizer (VM; Aerogen Solo; Aerogen Ltd, Galway); a jet nebulizer (JN; Oxycare; Ceren Uretim A.S., Istanbol, Turkey); or a metered dose inhaler (Ventoline, GlaxoSmithKline, Egypt) with an AeroChamber Vent spacer (Trudell Medical International, Canada). Both VM and JN groups received 5000 μg of salbutamol respiratory solution (Farcolin, 5000 μg/mL; Pharco Pharmaceuticals, Egypt) with a dose volume of 2 mL. The metered dose inhaler with spacer (MDI-AV) group received 1600 μg (16 actuations at 100 μg per puff) of salbutamol. For each experiment the MDI was shaken well and primed with 2 actuation prior to use, with >30 s intervals between actuations. All devices were placed in the inspiratory limb of mechanical ventilation circuit (Int'air medical, Bresse, France) downstream from the humidifier (VH 2100 humidifier with humidifier chamber; Great Group Medical Co. (GGM), Changhua County, Taiwan).

Subjects were randomized to receive aerosol during conventional mechanical ventilation with and without heated humidification at >24 h intervals with >12 h washout prior to each salbutamol dose. Salbutamol administration was withheld for at least 12 h prior dosing with salbutamol, with ipratropium bromide (Atrovent inhalation solution containing nominal dose of 25 μg mL^{-1}, Boehringer Ingelheim, Egypt) substituted during those periods.

According to previous reports.[21,24,26,29] using similar method, salbutamol was totally cleared from the urine after 24 h.

Urine samples were collected 15 min before each study dose to establish baseline and again at 0.5 h (USAL0.5) after dose completion. Urine was then collected over the next 24 h (USAL24). All samples were measured and assayed for salbutamol using HPLC. Salbutamol was extracted from urine samples using solid phase extraction with Oasis MCX cartridge (Waters corporation, USA), with bambuterol hydrochloride added as an internal standard, and then injected into HPLC system.[29] An ODS 5 μm, (4.6 × 250 mm, ZORBAX Eclipse) C-18 HPLC column with (4 mm × 3 mm, Agilent, USA) C-18 (ODS) guard column was used. Mobile phase, acetonitrile: water containing 0.1% orthophosphoric acid (90:10, v/v), was pumped through columns at a flow of 1 mL min^{-1} maintained at 25 °C and photodiode array detection was set at 220 nm. Limit of detection and lower limit of quantification for salbutamol was 0.36 and 1.00 μg mL^{-1}, respectively.

One way ANOVA with the application of the least significant difference (LSD) correction was used to determine differences between urinary salbutamol levels from the three inhalation methods with SPSS V17.0 (SPSS Inc., Chicago, USA). Independent T-test was used to determine difference between urinary salbutamol excretions at different humidity conditions ($p < 0.05$).

Results

36 (18 females) consented subjects receiving mechanical ventilation were enrolled and randomly assigned to one of the three treatment groups. All subjects completed both study doses.