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The relative lung and systemic bioavailability of terbutaline following nebulisation in non-invasively ventilated patients

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ABSTRACT

Nebulising a bronchodilator during non-invasive ventilation (NIV) is effective but there is a lack of consensus on the system to use because comparator in vivo studies in these patients are difficult. Urinary pharmacokinetic methodology post inhalation could provide this information. Chronic obstructive pulmonary disease patients requiring NIV received randomised study doses of either 2 mg terbutaline nebulised from an Aeroneb Pro (AERO) or 5 mg from a Sidestream (SIDE) on days 1 and 3 of admission. Urine samples were provided at 30 min then pooled up to 24 h post inhalation and amounts of urinary terbutaline (UTER0.5 and UTER24; indices of relative lung and systemic bioavailability, respectively) were determined. Twelve consenting patients receiving NIV mean (SD) age and weight of 74.8 (8.2) years and 61.0 (10.7) kg completed the study. The mean (SD) UTER0.5 following AERO and SIDE was 9.4 (3.7) and 10.4 (4.1) μg with a mean ratio (90% confidence interval) of 89.7 (87.8, 92.3)%. UTER24 was 192.3 (52.4) and 205.3 (58.0) mcg with a mean ratio (90% CI) of 93.7 (113.5, 77.3)%. This urinary pharmacokinetic method to identity relative lung and systemic bioavailability between two nebuliser systems was easy to perform and is a useful and simple in vivo method to compare different nebulisers in patients receiving non-invasive ventilation.

1. Introduction

Patients receiving non-invasive positive pressure ventilation (NIV) are prescribed inhaled bronchodilators for the relief of their airway obstruction. This can be provided to them by the use of a nebuliser or a pressurised metered dose inhaler (pMDI) in the circuit (Dhand and Tobin, 1997; Parkes and Bersten, 1997). When a nebuliser is used the system chosen is usually dictated by store availability due to the lack of published evidence about which is the most efficient system to use. This evidence is sparse because there is no simple method that could be used in comparator studies.

The European Respiratory Society has provided guidelines on the use and standardisation of nebulisers (Boe et al., 2001). These guidelines stress that the in vitro dose emission characteristics of the droplets aerosolised from different nebuliser systems should be equivalent. However such studies do not reflect how these systems perform during routine clinical practice. These in vitro studies have highlighted that there are differences between different nebuliser systems (Boe et al., 2001; Abdelrahim and Chrystyn, 2009; Berg et al., 2007) but the significance during patient use is not known. Patients receiving nebulised therapy range from stable patients with asthma and chronic obstructive pulmonary disease (as well as other chest diseases) to those with acute exacerbations of their respiratory disease. When these acute situations are likely to precipitate respiratory failure then their nebulised therapy is used with ventilatory support.

Each NIV system consists of a ventilator with tubing leading to a tight fitting face mask. In the tubing there is a leak port to allow air to escape during the patient's exhalation phase. Using in vitro methodology the optimal settings for aerosol delivery in patients receiving NIV have been investigated (Abdelrahim et al., 2010; Branconnier and Hess, 2005; Calvert et al., 2006; Chatmongkolchart et al., 2002). These studies have shown that the position of the leak port can affect the amount and quality of the emitted dose from a nebuliser (Abdelrahim et al., 2010; Calvert et al., 2006; Chatmongkolchart et al., 2002).

Lung deposition in patients receiving mechanically assisted invasive ventilation has been investigated using gamma scintigraphy (Harvey et al., 1997; O'Riordan et al., 1992; Fuller et al., 1994) and pharmacokinetic methodologies based on plasma salbutamol

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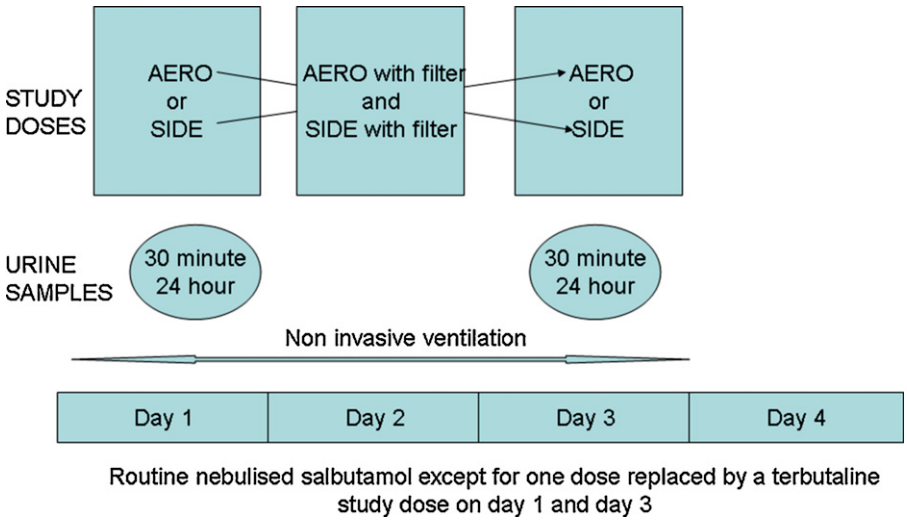

Fig. 1. Schematic design of the study.

concentrations (Duarte et al., 1996) as well as an ex vivo method (O'Riordan et al., 1994; O'Doherty et al., 1992; Fink et al., 1999). The set-up procedures and specialized equipment as well as inconvenience limit the use of these methods and they have not been used in patients receiving non-invasive ventilation. Ex vivo methods use a filter placed between the dose emission outlet and the patient's mouth and so gives no information about lung deposition (O'Riordan et al., 1994).

A urinary pharmacokinetic method has been shown to indicate the relative lung and systemic bioavailability of salbutamol following inhalation (Hindle and Chrystyn, 1992). These indices are based on the amount of salbutamol excreted in the first 30 min and over a 24 h period post inhalation (Hindle and Chrystyn, 1992). This pharmacokinetic method has been used following jet nebulisation of salbutamol to healthy volunteers (Silkstone et al., 2002a) and patients admitted with an acute exacerbation of either their asthma or their COPD (Mazhar et al., 2008). We have shown that this method also applies to terbutaline (Abdelrahim et al., 2011) and our analysis method differentiates between these two drugs (Mazhar and Chrystyn, 2009). Thus terbutaline can be substituted for a routine salbutamol dose in patients so that different inhalation methods can be studied without interfering with their bronchodilator therapy (Abdelrahim et al., 2011).

The aim of this study was to determine the feasibility of using this urinary pharmacokinetic method to compare relative lung and systemic deposition of different nebulisers in patients receiving NIV.

2. Materials and methods

2.1. Patients

Local hospital research ethics committee approval was obtained. Patients with a previous diagnosis of chronic obstructive pulmonary disease (COPD) that had been admitted to the Respiratory Unit with an acute exacerbation of their COPD and required NIV for respiratory acidosis ($PaCO_2$ > 6.0 kPa and pH < 7.35) were recruited into the study. They were all prescribed nebulised salbutamol on admission. All patients were recruited using a hospital approved delayed consent procedure.

Patients were ineligible to be included in this study if they had taken part in a research study during the previous 6 months, had a known hypersensitivity to terbutaline or salbutamol, a systolic blood pressure of <100 mmHg or severe renal impairment defined as a Creatinine Clearance or eGFR of <20 ml min^{-1}.

2.2. Study design and procedures

Bi-level ventilators are designed to provide airway support during breathing by blowing air into the airways during a breathing cycle. Pressure is increased during the patient's inhalation to a set level and allowed to decrease to a threshold level when they breathe out thereby reducing the work of breathing. The bi-level ventilator (B&D Electromedical, UK) was set in spontaneous mode at an inspiratory pressure of 20 cmH_2O and expiratory pressure of 5 cmH_2O according to the routine ward protocol. These ventilator pressures are the typical levels used for COPD patients. A schematic design of the study is shown in Fig. 1. The study doses were

- 5 mg (in 2 ml) of terbutaline sulphate respiratory solution (Bricanyl Respules containing a nominal dose of 2.5 mg ml^{-1}; AstraZeneca) with 2 ml 0.9% saline for nebulisation was nebulised, until sputtering, using a Sidestream jet nebuliser attached to a PortaNeb compressor (Philips Respironics, UK) [SIDE].
- 2 mg (in 0.8 ml) of terbutaline sulphate respiratory solution was nebulised to dryness using an Aeroneb Pro (Aerogen, IRL) vibrating mesh nebuliser [AERO].

Our in vitro dose emission studies (Abdelrahim et al., 2010) comparing these two nebuliser systems using methodology to replicate NIV identified that a 2 mg dose in AERO would provide a similar nebulised dose as a 5 mg dose from SIDE. Also during this preliminary in vitro work the position of the leak port was optimised (Abdelrahim et al., 2010). It was found that when the leak port was placed between the nebuliser and the ventilator that the emitted dose (and the fine particle dose) was greater. The schematic design in Fig. 2 shows that the configuration was the ventilator, leak port, nebuliser and the patient. Day 1 study doses occurred between 12 and 24 h after the start of NIV.

Patients entered a cross-over study and were randomised (using the toss of a coin) to the terbutaline study dose on day 1 nebulised using either SIDE or AERO and then from the other nebuliser system on day 3 (Fig. 1). The patients received their terbutaline sulphate study doses in place of their afternoon salbutamol dose.

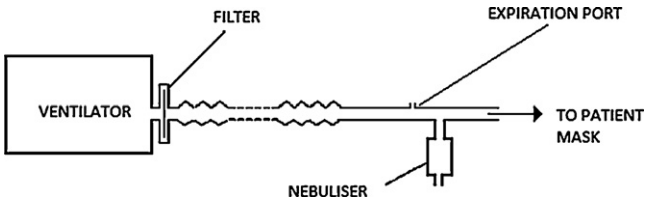

Fig. 2. Schematic design of the nebuliser positions within the non-invasive circuit bi-level ventilator. The inspiratory filter was placed as shown in the circuit in the ex vivo part of the study only.

Patients voided their urine 15 min before each study dose and then provided a urine sample 30 min (UTER0.5) from the commencement of nebulisation. Their urine was then pooled for the next 24 h (UTER24). The volume of the voided sample together with those of the 30 min and 24 h collection samples was measured and each sample was assayed using High Performance Liquid Chromatography (HPLC) to determine the terbutaline concentration. All parts of the non-invasive ventilation tubing and the nebuliser were rinsed with water and assayed by HPLC.

2.3. Ex vivo method

Fig. 1 shows that on day 2 subjects also received both study doses with a filter (Filta Guard breathing filter, Intersurgical limited, UK) placed between their NIV facemask and the nebuliser. Preliminary work had identified that this filter would entrain the entire dose that would be delivered to the facemask. This ex vivo method was used to identify the total dose that the patient would have received from each of the nebuliser systems studied. Since the patient would not have received any terbutaline from these study doses, because it would have all been captured on the filter, then their scheduled salbutamol administration was not replaced (see Fig. 1). Drug entrained on the filter was desorbed (TERF) and amounts left in the nebuliser system were recovered by rinsing then assayed using HPLC.

2.4. HPLC method

Terbutaline was extracted from the urine samples using solid phase extraction, with Bamethane added as the internal standard, then injected into the HPLC system. An ODS 5 μm (4.6 mm × 250 mm, Zorbax, Phenomenex) C-18 HPLC column with a (4 mm × 3 mm, Phenomenex) C-18 (ODS) guard column was used. The mobile phase, acetonitrile:methanol:tetrahydrofuran:ethyl acetate:buffer 5:5:5:5:80%, v/v, was pumped through the column at a flow of 1 ml min^{-1}. The column was maintained at 30 °C and fluorescence detection (excitation/emission of 267/313 nm) was used. The buffer was 40 mM phosphate buffer and 27.5 mM sodium dodecyl sulphate and adjusted to a pH of 6.75 using 10 mM potassium hydroxide. The limit of detection (LOD) and lower limit of quantification (LLOQ) for terbutaline was 24.2 μg/L and 73.4 μg/L, respectively.

2.5. Data analysis

Two way analysis of variance (ANOVA) was used to determine any difference between the urinary excretions from the inhalation methods. To identify equivalence between the inhalation methods UTER0.5, UTER24 and TERF amounts were log transformed and then analyzed by ANOVA. The ANOVA model used patients and the inhalation method as the main factors to calculate the mean ratio (90% confidence interval).

Table 1
Mean (SD) urinary excretion of terbutaline and the amount of terbutaline sulphate left in the nebulisers' post nebulsation ($n = 12$).

Nebuliser	UTER0.5	UTER24	Nebuliser
Amount (μg)			
AERO	9.4 (3.7)	192.3 (52.5)	1087.6 (98.0)
SIDE	10.4 (4.1)*	205.3 (58.0)	2615.9 (200.8)*
Amount (% nominal dose)			
AERO	0.57 (0.23)	11.71 (3.19)	54.6 (4.6)
SIDE	0.25 (0.10)*	5.00 (1.41)*	52.5 (4.3)

Nebuliser – amount left in the nebuliser at the end of the nebulisation.
* $p < 0.001$. AERO vs SIDE otherwise N/S, nominal dose is reported as terbutaline sulphate so the urinary amounts are normalised for the terbutaline content.

3. Results

3.1. Patients

All twelve (six females) NIV patients, mean (SD) age, weight and height of 74.8 (8.2) years, 61.0 (10.7) kg and 169.8 (12.4) cm, that were recruited agreed to be included using the delayed consent procedure and they completed all study doses. Four of the patients were catheterised. According to routine ward management of these patients spirometry is not measured for these patients and so was not done because of their condition.

3.2. Urinary terbutaline excretion

No terbutaline was detected in the voided pre study dose urine samples. The mean (SD) UTER0.5 after AERO and SIDE is presented in Table 1. Individual values are shown in Fig. 3 as (a) amounts and (b) expressed as a percentage of the nominal dose. The mean difference (95% confidence interval) between AERO and SIDE was −1.1 (−0.7 to −1.4; $p < 0.001$) μg and the mean ratio

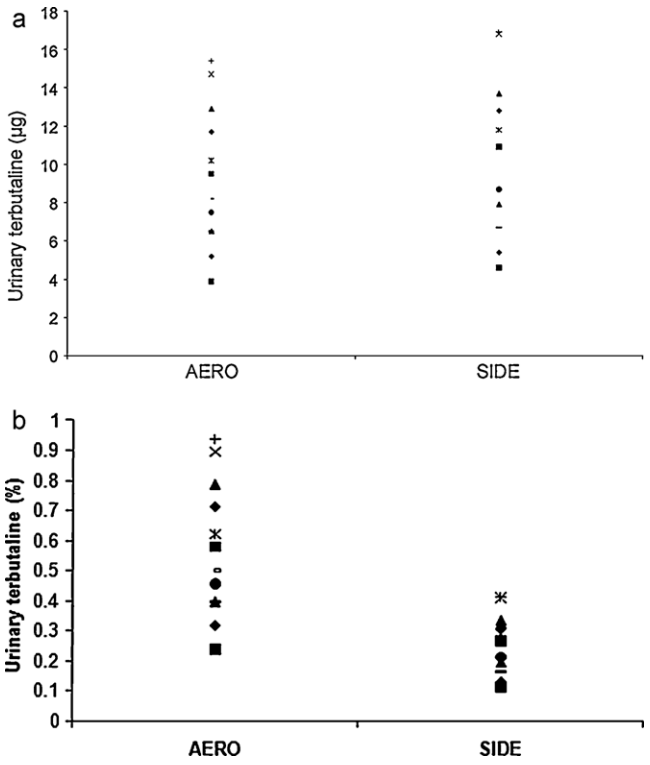

Fig. 3. Individual amounts of urinary terbutaline excreted 30 min (UTER0.5) post 5.0 mg terbutaline sulphate dosing via Sidestream jet nebuliser and 2 mg terbutaline sulphate via Aeroneb Pro, expressed in (a) amounts and (b) percentage of the nominal dose.

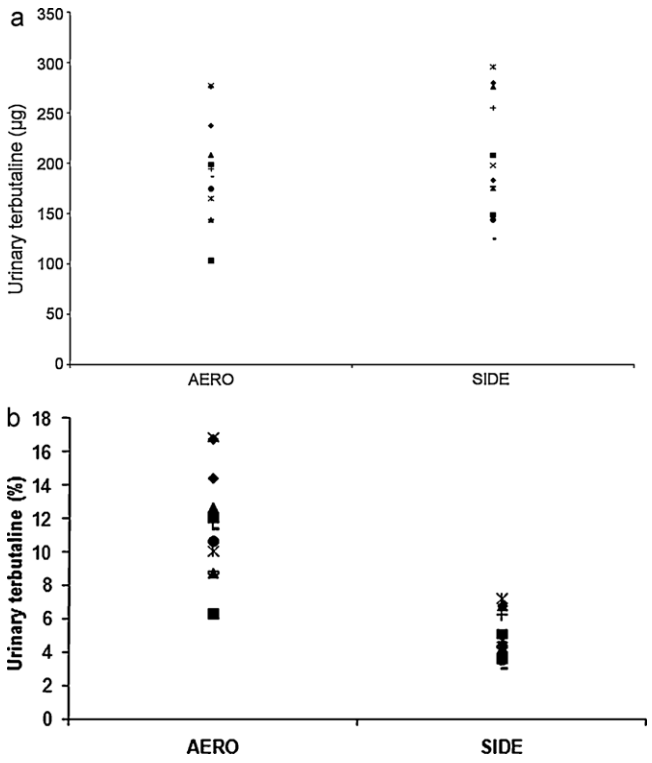

Fig. 4. Individual amounts, in µg of urinary terbutaline excreted in the first 24 h (UTER24) post 5.0 mg terbutaline sulphate dosing via Sidestream jet nebuliser and 2 mg terbutaline sulphate via Aeroneb Pro, expressed in (a) amounts and (b) percentage of the nominal dose.

(90% confidence intervals) for the amounts excreted between the two nebuliser systems was 89.7 (87.8, 92.3)% thereby identifying equivalence in the relative bioavailability to the lungs following inhalation using the two nebuliser systems. Table 1 also shows that although there is a difference ($p < 0.001$) between the residual amounts left in the nebuliser chamber this is due to the nominal dose and the expected large residual amounts of jet nebulisers.

The mean (SD) UTER24 is presented in Table 1 with a comparison of individual amounts in Fig. 4. The mean difference was −13.0 (−60.8, 34.7) µg and the mean ratio (90% confidence interval) was 93.7 (77.3, 113.5)% which confirms the equivalence in the relative bioavailability to the body following inhalation using the two nebuliser systems.

6 (3 females) NIV patients received their terbutaline nebulised dose from AERO on day 1 compared to 6 (3 females) that received SIDE first. Statistical analysis of UTER0.5 and UTER24 on day 1 compared to day 3 (irrespective of nebulisation method) was similar with a mean difference (95% confidence interval) of 0.2 (−0.6, 1.0) µg and of 8.9 (−39.3, 57.1) µg, respectively.

3.3. Ex vivo study

The fate of the nebulised dose during the ex vivo study is presented in Table 2. This shows that the amounts entrained on the filter, representing the dose the patient would have received exiting the system into the facemask, were different with a mean ratio (90% confidence interval) of 68.4 (61.6, 75.9)% for AERO compared to SIDE. Consistent with the urinary pharmacokinetic study the residual amount of terbutaline in SIDE was greater than AERO ($p < 0.001$).

4. Discussion

The results demonstrate the feasibility of using this urinary pharmacokinetic method to compare the relative lung and systemic bioavailability of different nebulisers in patients even when their breathing is severely compromised. The use of terbutaline respirator solution as a study dose in place of their prescribed salbutamol allows a patient's therapeutic routine management to be uninterrupted while the performance of the two nebulisers is compared. A mean ratio with 90% confidence limits between 80 and 125% is regarded as demonstrating bioequivalence for inhaled products (Guideline E, 2008). Hence when 2 mg of terbutaline respiratory solution was nebulised in an Aerogen Pro the relative lung (urinary terbutaline excretion in the first 30 min) and systemic (urinary excretion over the 24 h period post inhalation) delivery was equivalent to 5 mg nebulised using the Sidestream jet nebuliser. The study highlights that this urinary pharmacokinetic method is simple to implement with minimal inconvenience during routine patient management and provides sufficient in vivo data to compare different nebuliser systems. At present there is no other non-invasive method to compare the performance of nebulisers using a realistic setting.

The results also consolidate the ERS Consensus Statement (3) for the availability of comparative information when managing patents with different nebuliser systems. Without this data then during routine practice the same dose would be used irrespective of the nebuliser system. Hence a patient would receive 5 mg nebulised using a Sidestream and an Aerogen Pro. Although it is unlikely that there would be no difference in the bronchodilation between 2 and 5 mg nebulised from the Aerogen Pro, due to the shallow dose–response relationship, the greater systemic delivery could be significant especially with respect to heart rate and electrolyte levels.

Clinical studies to compare different inhalation methods are the gold standard but are not practicable when patients require non invasive ventilation and standard spirometry would provide low responses (Nava et al., 2001). Spirometry, therefore, is not routinely measured in this unit when a patient receives NIV. Even in acute exacerbations of either asthma or COPD when NIV is not indicated spirometry provides minimal changes in these patients (Mazhar et al., 2008).

Lung deposition studies are an alternative to clinical studies but have not been reported in patients receiving NIV. Although studies in mechanically ventilated patients have reported methods based on gamma scintigraphy (Harvey et al., 1997; O'Riordan et al., 1992; Fuller et al., 1994) as well as plasma salbutamol (Duarte et al., 1996), to compare nebulisers by these methods presents many practical and logistic issues especially when the patient is very ill. These include interrupting the NIV therapy, moving the patient to a gamma camera and administering a radioactive labelled formulation of the bronchodilator or taking numerous blood samples soon after the start of nebulisation. Although the collection of urine samples, for the urinary pharmacokinetic method, does present problems they did not interfere with the management of the patients, did not cause inconvenience and were readily provided when required. Frequently these patients are catheterised which makes the collection of these urine samples more convenient. Furthermore the use of a different bronchodilator as the study dose, which is substituted for one of their regular doses, does not interfere with their routine bronchodilator management. Previous studies have used this urinary pharmacokinetic method to identify the relative lung and systemic bioavailability when salbutamol was nebulised by the same jet nebuliser (Sidestream) using volunteers (Silkstone et al., 2002b) and patients admitted with an acute exacerbation of either asthma or COPD (Mazhar et al., 2008). The mean urinary drug excretion over the first 30 min in the volunteers was 0.64% of the nominal dose (Silkstone et al., 2002b) compared to 0.28 and 0.29% in the acute asthmatics and COPD patients (Mazhar et al., 2008). These values in the COPD and asthma patients with acute exacerbations are similar to the 0.25% in these

Table 2
Mean (SD) amount of terbutaline sulphate recovered from the filter, T-piece and nebuliser's chamber from the day 2 ex vivo ($n = 12$).

Method	Amount in μg			TERF (% nominal dose)
	Filter (TERF)	T-piece	Nebuliser	
AERO	771.7 (42.7)	214.3 (39.6)	844.3 (115.9)	38.6 (2.3)
SIDE	1140.6 (186.7)	347.5 (127.4)	2463.7 (749.6)	22.8 (4.0)

patients receiving NIV. These low values are consistent with the reduced lung deposition due to their airway limitation (Lipworth and Clark, 1997). Although it could be anticipated that lung deposition in patients requiring NIV would be lower this could have been offset by the positive pressures, during the inhalation phase, driving more of the aerosolised dose into the lungs. We did not investigate the effect of different inspiratory and expiratory pressure settings to explore this because it is standard procedure to use NIV for only 72 h.

The 24 h urinary drug excretion represents the total systemic delivery (Hindle and Chrystyn, 1992). The urinary drug excretion after inhalation from the Sidestream jet nebuliser is the same as that previously reported in patients with an acute exacerbation of asthma and COPD (Mazhar et al., 2008) and half of that excreted by volunteers (Silkstone et al., 2002b). Hence these results mimic those of the relative lung deposition. The ratios of the 30 min and 24 h urinary drug excretions are all of the same magnitude in these NIV patients as the patients with acute exacerbations of asthma and COPD (Mazhar et al., 2008) and volunteers (Silkstone et al., 2002b).

The first dose was started soon after the start of their NIV therapy on day 1 of their admission and they gradually improved over the next 3 days. All patients recovered and were successfully taken off ventilatory support by day 4. It is understandable to assume that their physical and physiological characteristics would be different. However there was no difference between their day 1 and day 3 30 min urinary terbutaline excretions thus their lung deposition did not change. Since lung deposition (Lipworth and Clark, 1997) has been reported to be related to airway calibre then there is no explanation for no difference in the relative lung deposition even though the number of patients is low. This lack of a difference between day 1 and 3 is consistent with that we have previously reported for this urinary pharmacokinetic method using patients admitted with an acute exacerbation of either their asthma or their COPD (Mazhar et al., 2008). If there would have been a difference, due to the change in the status of their airways, then this method would not be valid during acute exacerbations with or without NIV. The lack of detectable terbutaline pre day 3 study dose shows that the short washout period was sufficient.

In a previous study we used in vitro methodology with the same bi-level ventilator to simulate NIV and a breathing simulator in place of the patient. This in vitro study revealed that the mass median aerodynamic diameter of the droplets aerosolised by the two systems was similar and the emitted dose was approximately 2.5 times greater from the Aeroneb Pro. Likewise the fine particle dose was greater. It was this in vitro study that decided the different doses we have used. This difference between jet and vibrating mesh nebulisers is consistent to those previously reported (Dubus et al., 2005; Fink et al., 2001) and highlights the need to use a lower drug dose when switching a patient to these new generations of nebulisers.

The similarities of the relative lung and systemic bioavailabilities in these NIV patients to the in vitro results (Abdelrahim et al., 2010) supports the possibility of in vitro/in vivo correlations. We have previously reported such correlations when we determined the relative lung and systemic bioavailability of salbutamol and the in vitro characteristics of their emitted doses when nebulised by 8 different nebuliser systems (Mazhar et al., 2008). These correlations together with other evidence of lung deposition to in vitro data (Newman and Chan, 2008) highlight that a strong link exists between the fine particle dose and the total emitted dose (measured by in vitro methods) to lung deposition and systemic delivery, respectively.

Previous studies have shown the value of ex vivo methods to compare different nebuliser systems (O'Riordan et al., 1994; O'Doherty et al., 1992; Fink et al., 1999). This method uses a filter placed in the tubing immediately before the facemask. The filter entrains the entire dose so that none of it reaches the patient. Hence this is a convenient method to determine the dose that would have entered the facemask. Since the filter takes out the entire dose then on day 2 patients received their normal routine nebulised doses (as shown in Fig. 1). The amount entrained on the filter when these NIV patients received their nebulised dose from the Sidestream was almost 1.5 times greater than that from the Aeroneb Pro. This is not consistent with the in vitro data we have previously reported (Abdelrahim et al., 2010) or with the 24 h urinary terbutaline excretion results. Whether this is difference is due to the practicalities of this method or that it does not reflect the amounts the patients inhaled is not known. Due to these differences our results suggest that the ex vivo method is not reliable.

5. Conclusions

The urinary pharmacokinetic method using 30 min post inhalation and cumulative 24 h urinary drug excretion can be readily used in patients receiving NIV to compare different inhalation methods. The use of terbutaline study doses means each patient's bronchodilator therapy is maintained. This method could be applied to other nebulisers and provides a simple way to compare the in vivo performance of nebulisers during routine clinical use. The magnitude of the differences for both these indices (relative lung and systemic bioavailability, respectively) between the two nebuliser systems highlights the importance to make these comparisons rather than assume that they are equivalent. Vibrating mesh nebulisers are more efficient to administer aerosols to the mechanically ventilated patient.

Contributor

Professor Chrystyn has full access to all of the data in the study and he takes full responsibility for the integrity of all of the data and the accuracy of the data analysis, including and especially any adverse effects. M.E. Abdelrahim was supported by a Government of Egypt Scholarship.

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