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Research Paper

In-vitro characterisation of the nebulised dose during non-invasive ventilation

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Abstract

Objectives Non-invasive ventilation (NIV) with nebulised bronchodilators helps some patients to maintain effective ventilation. However, the position of the nebuliser in the ventilation circuit may affect lung delivery.

Methods We placed the nebuliser proximal (A) and distal (B) to a breathing simulator in a standard NIV circuit with inspiratory (I) and expiratory (E) pressures of 20 and 5 cm H_2O, 1 : 3 I : E ratio, 15 breaths/min and a tidal volume of 500 ml. Five milligrams of terbutaline solution was nebulised using an Aeroneb Pro (AERO) and a Sidestream (SIDE) nebuliser. The fate of the nebulised dose was determined and the aerodynamic droplet characteristics were measured using a cooled Next Generation Impactor.

Key findings More terbutaline was entrained on the inhalation filter in position A than in position B ($P < 0.001$) for both nebulisers. These amounts were greater ($P < 0.001$) for AERO than SIDE due to a smaller ($P < 0.001$) residual volume. The mean (SD) fine particle doses for AEROA, AEROB, SIDEA and SIDEB were 1.31 (0.2), 1.13 (0.14), 0.56 (0.03) and 0.39 (0.13) mg. These amounts from AEROA were significantly greater ($P < 0.001$) than those of the other three methods.

Conclusions The results highlight the differences between nebulisers and the influence on the placement of the nebuliser in the NIV circuit.

Keywords aerodynamic characteristics; nebuliser; Next Generation Impactor; non-invasive ventilation; terbutaline

Introduction

Mechanical ventilation provides effective support to patients with an acute exacerbation of their chronic obstructive pulmonary disease (COPD) that have a respiratory acidosis.[1] Mechanical ventilation is either non-invasive (NIV) with a face or nasal mask or it is invasive. Paralysis, sedation and endotracheal intubation are required for invasive ventilation. It has been reported that NIV reduces intubation rates and improves mortality compared to conventional medical therapy.[2]

Therapeutic aerosols are commonly used in mechanically ventilated patients.[3–5] These agents are delivered by nebulisers or a pressurized metered dose inhaler p(MDI) attached to a spacer adapted for use in ventilator circuits. Studies using patients with stable asthma[6] and COPD[7] have confirmed that aerosol delivery during NIV is feasible and effective.

Objective clinical response, for example standard spirometry, is difficult in patients receiving NIV so an in-vivo clinical comparison of different systems is difficult. The European Respiratory Society has issued guidelines on the use of nebulisers that have highlighted the need to compare and optimize nebuliser performance.[8] These guidelines highlight the need to use in-vitro methods to identify the dose emitted from a nebuliser because it has been reported that the aerodynamic droplet characteristics of the aerosolised dose can vary from jet nebulisers for different flow rates, compressors and volumes.[9] Vibrating mesh nebulisers provide a dose emission that is 2.5 times greater than a jet nebuliser.[10,11]

In-vitro studies, using circuits to mimic NIV, have investigated the position of the nebuliser and the expiration port as described in Figure 1. The first study revealed that delivery of the nebulised dose to the inhalation outlet was dependent on the position of the expiration port, the ventilator settings and the breathing rate.[12] This demonstrated that a

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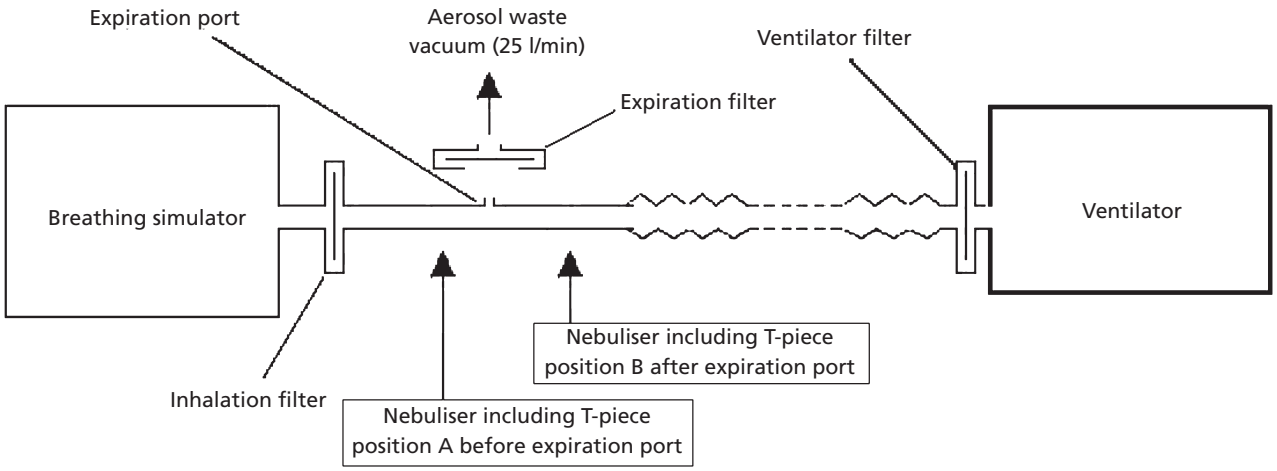

Figure 1 Schematic design of the in-vitro non-invasive method used to determine the fate of the nebulised dose.

nebuliser placed in the NIV circuit can deliver a significant mass of drug when placed next to the breathing simulator. This is similar to position A in Figure 1. Calvert *et al*. have shown that placing the nebuliser in this position was the most inefficient position.[13] In contrast to Chatmongkolchart *et al*.[12] Calvert found that placing the expiration port proximal to the breathing simulator (position B in Figure 1) provided greater delivery. Branconnier and Hess have reported that an expiration port in the face mask provided the greatest delivery of salbutamol when it was nebulised.[14] All other in-vitro studies comparing nebulisers have used circuits that mimic invasive ventilation.

Calvert *et al*. used a breathing simulator based on a single pump system (the Pari Compass; Pari, GmbH),[13] whereas Chatmongkolchart *et al*. and Branconnier and Hess used a dual chamber test lung.[12,14] All of these studies used jet nebulisers and have focused on the total output, although Calvert did reveal that droplets were smaller with the ventilator turned on, which could be due to evaporation effects within the NIV tubing. Using in-vitro circuits to mimic invasive ventilation it has been reported that there are differences in the output and performance between the vibrating mesh nebulisers and jet nebulisers[10,11] as well as ultrasonic devices.[15] As part of our in-vitro and in-vivo programme on bronchodilator delivery to NIV patients we have therefore determined the in-vitro dose emission properties (including droplet aerodynamic characteristics) of a jet nebuliser and one that uses a vibrating mesh principle. We have sited the expiration port proximal and distal to the breathing simulator and for both positions have placed the nebuliser as close as possible to the breathing simulation to mimic routine care.

Materials and Methods

Nebuliser systems

A quantity of 5 mg (in 2 ml) of terbutaline sulfate respiratory solution (Bricanyl Respules containing a nominal dose of 2.5 mg/ml; AstraZeneca, UK) was nebulised using the Aeroneb Professional (AERO) Nebuliser System (Aerogen Inc., Ireland) and the Sidestream (SIDE) nebuliser attached to a PortaNeb compressor (Philips Respironics, UK). The PortaNeb compressor provides an air flow of 6 l/min into the nebuliser to aerosolise the liquid. AERO is a vibrating mesh nebuliser and SIDE is a jet nebuliser.

In-vitro fate of the nebulised dose using a biventilation system for non-invasive ventilation

Each of the two nebuliser systems (previously described) was assembled according to Figure 1, an arrangement that was designed to mimic that of a patient receiving NIV. This methodology is an adaptation of the CEN method to determine the fate of a nebulised dose using sinus flow breath simulation.[16] Instead of using a fluoride tracer, as recommended by CEN, we determined the mass of terbutaline sulfate.

A quantity of 2 ml of terbutaline sulfate was added to the chamber of each nebuliser. A breathing simulation machine (Compass; Pari GmbH, Germany) was connected to a bilevel ventilator (Nippy2; B&D Electromedical, UK) as shown in Figure 1. The NIV breathing circuit consisted of a 180 cm length of corrugated tubing (diameter 22 mm) and a fixed leak expiration port (B&D Electromedical, UK). Spontaneous breathing was simulated to represent that of a typical adult with COPD and thus provided a tidal volume of 500 ml with a rate of 15 breaths per minute and inspiratory to expiratory phase ratio of 1 : 3. The bilevel ventilator was set in spontaneous mode at an inspiratory pressure of 20 cm H_2O and expiratory pressure of 5 cm H_2O. The breathing simulator triggered the bilevel ventilator. The ventilator pressures were chosen as typical of the levels used in COPD patients when NIV is prescribed during acute exacerbations at local hospitals. The outlet of each nebuliser was attached to its standard T-piece and both outlets were connected into the NIV circuit tubing with a tight seal.

An electrostatic filter pad (Pari GmbH, Germany) enclosed in a filter holder (Pari GmbH, Germany) was attached next to the breathing machine (inhalation filter). This filter entrains all the aerosol produced during the inhalation period of a

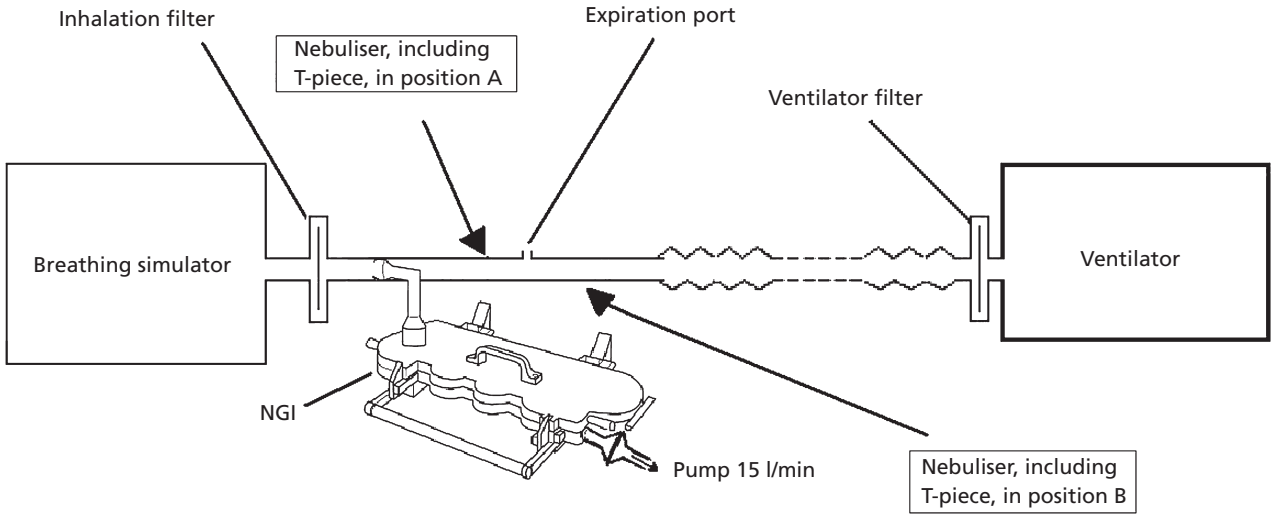

Figure 2 Schematic design of the methodology for measuring the aerodynamic characteristics of the aerosolised dose with the non-invasive circuit. NGI, Next Generation Impactor.

breathing cycle and thus provides a good measure of the total inhaled aerosol dose (the in-vitro emitted dose available for inhalation). Another electrostatic filter was attached next to the ventilator (ventilator filter) to check if any aerosol reached the ventilator. A third electrostatic filter was placed 4 cm above the outlet of the expiration port of the NIV system (expiration filter). A vacuum of 25 l/min was drawn through this filter to ensure that it captured the entire dose that was expelled from the NIV system.

The nebuliser position was varied within the ventilator circuit between position A (AEROA and SIDEA) and position B (AEROB and SIDEB), as shown in Figure 1. In position A the nebuliser was proximal to the breathing simulator. In position B the expiration port was proximal to the breathing simulator. The distances between the nebuliser and the inspiratory filter were 8 cm and 10 cm for positions A and B, respectively. The breathing machine and ventilator were switched on 30 s before the nebuliser. Terbutaline sulfate (5 mg in 2 ml) was nebulised to sputtering for the Sidestream jet nebuliser driven by the PortaNeb compressor and to dryness for the Aeroneb Pro nebuliser.

For each nebuliser system, 10 determinations were made ($n = 10$). The terbutaline sulfate entrained on each of the filters, left in the nebuliser chamber and deposited inside the tubing were recovered by rinsing with 25% acetonitrile. Amounts entrained on the filter were sonicated with 25% acetonitrile prior to rinsing. HPLC with fluorescence detection was used to quantify the terbutaline. The method used a 25 mm × 4.6 mm Spherisorb C18, ODS1 column (Waters, UK) through which a mobile phase of 5 mM potassium dihydrogen orthophosphate–acetonitrile (75 : 25), adjusted to pH 2.5 with orthophosphoric acid, was pumped at 1 ml/min. A fluorescence detector (RF-551, Shimadzu, Japan), set with an excitation/emission of 267/313 nm, was used with bamethane hemisulfate (Sigma, UK) as the internal standard. Calibration solutions ranged from 25 to 800 μg/l (w/v). The limit of detection was 10.9 μg/l and the lower limit of quantification was 33.1 μg/l. For nominal concentrations of 50, 300 and 700 μg/l the overall ($n = 75$) mean (SD) intra- and interday coefficients of variation were 2.8 (0.2) and 4.5 (0.1)%, respectively. Similarly the intra- and interassay accuracy ($n = 75$) were 96.5 (1.1) and 97.4 (2.7)%.

Aerodynamic particle size characterization using the Next Generation Impactor

A Next Generation Impactor (NGI; Copley Scientific Ltd, Nottingham, UK) was used to determine the particle droplet size distribution of the aerosolised drug that would be delivered to the patient. The NGI was cooled in a refrigerator at 4°C for 90 min before each determination and each determination was completed within the recommended 10 min of removal from the refrigerator.[17] The experimental set-up is described in Figure 2. This figure shows that positions A and B were the same as used in Figure 1 and that the NGI was always proximal to the breathing simulator (close to the inhalation filter) to sample the aerosol that was emitted (which would represent the aerosolised dose delivered to a patient's mouth during an inhalation). The distances between the nebuliser and the inspiratory filter were 15 and 17 cm for positions A and B respectively and those between the nebuliser and the impactor were 8 and 10 cm, respectively.

All the parts of the NGI were washed in methanol and allowed to dry. The collection cups were not pre-coated with any agent to provide a tacky surface, as it has been recommended recently by the European Pharmaceutical Aerosol Group (EPAG) that collection cups do not require coating for nebuliser aerosol assessments.[18,19] The NGI was assembled without the preseparator. The micro-orifice collector (MOC) is ineffective for holding the very small aerosol droplets when the NGI is operated at 15 l/min,[17,20] therefore a back-up filter (Pari GmbH, Germany) was placed after the MOC. The NGI, with the plates *in situ*, was placed in a refrigerator at 4°C for 90 min before use.[21] Hence the induction port of the NGI was connected directly into the NIV circuit with an airtight seal. The vacuum flow through the NGI apparatus was provided by a GAST pump (Brook Crompton, UK). The flow rate was

measured using an electronic digital flow meter (MKS Instruments, USA) and a critical flow controller, model TPK (Copley Scientific Ltd, UK). Parafilm M laboratory film (Pechiney Plastic Packaging, USA) was used to seal the apparatus.

For each set of operating conditions, five separate determinations were made for each nebulised system. For each determination the NIV system was operated for 30 s before the start of the nebulised dosing. Nebulisation continued to dryness when using the Aeroneb Pro and to sputtering with the Sidestream. At this point the vacuum pump of the NGI and the NIV system were switched off. Terbutaline deposited on each plate of the NGI and the nebuliser system (chamber and tubing) was recovered by rinsing with 25% acetonitrile, as described above. Similarly, the mass entrained on the filters was recovered by sonication and rinsing. The mass deposited on each plate, entrained on the filters, deposited in the tubing and remaining in the nebuliser system were determined by high-performance liquid chromatography as previously described.

Data analysis

Copley Inhaler Testing Data Analysis Software (CITDAS, Copley Scientific, Nottingham, UK) impactor data analysis software was used. The log cumulative percentage undersized was plotted on a probability scale against the log of the aerodynamic diameter for the cut-off values of the NGI stages. The spread of each aerodynamic particle size distribution was unimodal and log normal. From the log-probability plot, the fine-particle dose (FPD) was the mass of terbutaline sulfate that contained droplets <5 μm in aerodynamic diameter. The fine particle fraction (FPF%) was the FPD divided by the total mass that was deposited into the throat and stages of the NGI. The MMAD was the diameter corresponding to 50% undersized and the geometric standard deviation (GSD) was determined as the square root of the ratio of the 84.1 to 15.9 mass percentiles of the aerodynamic particle size distribution.

Statistical analysis

All data are expressed as mean ± standard deviation. One-way ANOVA with the application of the Bonferroni correction was used to compare the position of the nebuliser with respect to the expiration port. This method was also used to compare the two nebulisers.

Results

Table 1 provides a summary of the fate of the nebulised dose. No terbutaline was recovered from the ventilation filter or the tubing between this filter and either the expiration port for position A or the nebuliser for position B. More ($P < 0.001$) terbutaline was entrained on the inhalation filter than was captured escaping from the expiration port for the AERO A methodology. For the other three methods more ($P < 0.001$) was captured leaving the expiration port than was entrained on the inhalation filter. Statistical analysis between the four methods revealed that there was a highly significant ($P < 0.001$) difference in the amounts recovered on the inhalation filter, expiration filters and that remaining in the nebuliser chamber. Significantly ($P < 0.001$) more was entrained on the inhalation filter and less on the filter at the expiration port for AEROA compared to the other three methods. The residual volumes left in the chambers for AEROA and AEROB were similar, as well as SIDEA compared to SIDEB. Comparison of the residual volumes of AEROA to SIDEA and of AEROB to SIDEB revealed that less ($P < 0.001$) remained in AERO. The mean (SD) nebulisation times for AERO and SIDE were 222 (4.2) and 226.4 (26.3) s.

The aerodynamic droplet size distribution from each nebulised system is summarised in Table 2. Consistent with the above results, no drug was recovered on the ventilation filter or deposited in the tubing of the NIV circuit between the expiration port or the nebuliser and ventilator in method A and B, respectively. Statistical analysis for both the AERO and SIDE between positions A and B revealed no difference in the FPF or the MMAD. Comparison of position A between AERO and SIDE revealed that while the FPF of SIDE was higher ($P = 0.002$) and MMAD smaller ($P = 0.003$) the FPD from AERO was very much greater ($P < 0.001$) due to a smaller ($P < 0.001$) residual amount. Similar statistical results were obtained when comparing position B between the two nebulisers [FPF greater ($P = 0.002$), MMAD smaller ($P = 0.024$) for SIDE whilst FPD was much greater ($P < 0.001$) from AERO].

Discussion

Placing either the Aeroneb Pro or the Sidestream jet nebuliser between the breathing simulator and the expiration port (position A) produced a greater delivery of drug to the inhalation outlet and less was lost through the expiration port. During the inhalation phase the added positive pressure from the ventilator will direct air towards the patient (hence breathing simulator). For position A, therefore, all the dose that is aerosolised during the inhalation phase is directed to the inhalation filter. This is not the case for position B because some of the nebulised dose will be forced out of the expiration port because of

Table 1 Fate of terbutaline dose nebulised by Aeroneb Pro and Sidestream for positions A and B

	Inhalation filter (μg)	Tubing (μg)	Nebuliser (μg)	Expiration port filter (μg)
AEROA	2572.5 (150.9)	770.0 (260.7)	891.0 (162.7)	957.9 (257.8)
AEROB	935.5 (273.3)	979.5 (224.0)	1000.8 (262.5)	2416.0 (406.5)
SIDEA	1207.2 (161.3)	310.6 (130.2)	2260.6 (794.8)	1517.9 (148.6)
SIDEB	341.0 (69.5)	559.9 (76.0)	2419.7 (153.5)	2053.0 (173.0)

Figures for 5 mg dose are presented as means with SD in parentheses ($n = 10$). Figures in tubing column are quantities recovered from the nebuliser T-piece and the NIV tubing.

Table 2 Characteristics of aerosolised dose from an Aeroneb Pro and a Sidestream nebuliser for position A and B

	AEROA	AEROB	SIDEA	SIDEB
Chamber (μg)	626.0 (173.3)	581.5 (141.6)	1818.9 (100.4)	2123.2 (224.9)
Inhalation filter (μg)	522.1 (166.2)	437.3 (149.9)	203.3 (23.4)	162.2 (52.0)
T-pieces and expiration port (μg)	508.7 (151.1)	619.8 (297.8)	83.6 (27.0)	140.3 (23.8)
Throat (μg)	843.3 (71.1)	621.8 (94.9)	367.5 (191.9)	177.9 (104.1)
Total dose in the impactor (μg)	2228.7 (214.9)	1806.0 (233.3)	813.5 (46.2)	547.7 (168.2)
FPD (μg)	1314.4 (194.9)	1126.3 (142.5)	559 (32.5)	391.3 (132.0)
FPF (%)	58.8 (4.6)	62.4 (1.8)	68.8 (4.7)	72.2 (3.4)
MMAD (μm)	4.1 (0.4)	3.8 (0.2)	3.2 (0.3)	3.2 (0.2)
GSD	4.5 (1.7)	3.1 (1.8)	2.3 (0.1)	2.2 (0.1)

Figures are means with SD in parentheses ($n = 5$).
FPD, fine-particle dose; FPF, fine particle fraction; GSD, geometric standard deviation.

the placement of this port between the nebuliser and the inhalation filter. However, this does not explain all the results because we used an inhalation : exhalation ratio of 1 : 3 and the dose is aerosolised from each nebuliser continuously. During exhalation, therefore, more aerosol would be expected to be expelled from the expiration port in position A, but this was not the case.

During an exhalation, NIV maintains a positive pressure so that the patient's airways do not collapse when they breathe out. This positive pressure does enable exhaled air to leave the expiration port so that the patient breathes fresh air. However, the positive pressure is sufficient to prevent the total escape of the dose that is aerosolised during the exhalation phase. It is held inside the NIV circuit and, due to the small droplet size and because the maximum time for the exhalation phase would be 3 s, deposition due to gravity is not significant. When an inhalation starts, the dose left in the NIV circuit, which is nebulised during the exhalation phase, is directed towards the breathing simulator (hence the patient).

We did not detect any terbutaline on the ventilator filter or the tubing between this filter and either the expiration port in position A or the outlet of the standard T-piece nebuliser for position B. This was due to the internal volume of the NIV tubing of approximately 840 ml and we used a tidal volume of 500 ml together with the positive pressure during the exhalation phase. Also any loss via the ventilator in position B during the early exhalation phase, as reported by Chatmongkolchart *et al*,[12] did not occur because we placed the nebuliser much closer to the breathing simulator.

Our results for the position of the expiration port distal to the breathing simulator are consistent with those of Chatmongkolchart *et al*.,[12]who used a Micromist (Hudson) nebuliser. However, during routine care, if the nebuliser is placed distal to the patient, it would be much closer than the positions used by Chatmongkolchart and the rationale for this was confirmed by Calvert *et al*.[13] For positions A and B we have found that for the Sidestream jet nebuliser, 24 and 7% of the nominal dose was entrained on the inhalation filter and captured leaving the expiration port. In contrast, Calvert *et al*., using a Cirrus jet nebuliser, reported respective amounts of 8.5 and 13%.[13] They used an inspiratory : expiratory ratio of 2 : 3 compared to our 1 : 3 ratio, as well as a greater tidal volume and fewer breaths per minute. For these positions, our Aerogen Pro dose emissions of 51 and 18.7% for in-vitro NIV are consistent with the reported differences between jet and vibrating mesh nebulisers when using circuits to mimic invasive ventilation.[10,11]

The differences highlight how inhalation and exhalation conditions as well as the nebuliser and the position of the expiration port affect the dose that would be delivered to a patient prescribed NIV. The results also confirm the recommendations of the European Respirator Society to provide comparative data on all nebulised systems.[8] These guidelines recommend that the in-vitro aerodynamic characteristics of the emitted droplets aerosolised from a nebuliser should be determined by a Marple 298 Impactor. However, it has been shown that this method is prone to evaporation and hence lacks sufficient sensitivity to discriminate between different nebuliser systems.[21] We[21] and others[17,22] have shown that a cooled NGI should be used and that determinations should be completed within 10 min of taking the NGI from the refrigerator. Since nebulisation times are long, we used 2 ml for our determinations in a jet nebuliser. Our preliminary investigations revealed that when we diluted the terbutaline solution with 2 ml saline, the nebulisation time of the Sidestream was approximately 13 min. It has been shown that fill volume influences the residual amounts left in the chamber of a jet nebuliser[23] and this is the reason why the output was greater for the Aerogen Pro, which has a lower residual volume.

During the exhalation phase a majority of the nebulised dose is held within the NIV tubing and then directed to the patient during their inhalation. Hence this holding effect would be similar to that when a pressurised metered dose inhaler is used with a valve holding chamber (spacer). This should enhance evaporation effects and thus reduce the size of the droplets. The MMADs for the Aeroneb Pro and the Sidestream were found to be 4.1 and 3.2 μm, respectively. In a previous study using the same methodology and the classical nebulisation method (not using NIV) we reported respective MMADs of 5.0 and 4.2 μm for these nebulisers.[21] The FPF using the NIV circuit is also larger. These differences highlight that evaporation is occurring in the NIV circuit. This was also reported by Calvert *et al*.,[13] in that during NIV the MMAD from the Cirrus jet nebuliser was 2.21 μm and when they used the same system with the ventilator switched off the droplet size was 2.99 μm. The

smaller MMAD and hence higher FPF, together with the direction of the dose towards the patient during NIV, suggests that lung deposition in these patients would be more than when a patient receives a nebuliser using the conventional method.

The MMAD of the Aeroneb Pro in position B was smaller than in position A and the so the FPF was greater. This suggests that the evaporation effects were more pronounced due to the greater distance of the nebuliser from the NGI for position B. These aerodynamic parameters for the Sidestream were similar, irrespective of position. The difference in these effects may be due to the cooler temperature of the dose emitted from a jet nebuliser.[24,25]

Although the Sidestream MMADs were smaller, and hence the FPFs were greater than those of the Aeroneb Pro, the differences are small and therefore unlikely to be significant. However, the 2.4-fold higher fine particle dose for position A of the Aeroneb Pro compared to the Sidestream also in position A would provide much greater lung deposition and thus would be likely to be clinically significant. This large difference is due to the lower residual dose in the Aeroneb Pro. Although pulmonary clinical response would probably be at the top of the dose–response relationship, the important clinical effect would be from greater systemic exposure if the dose was not changed. This is substantiated by the 2.1-fold greater amount entrained on the inhalation filter (2572.5 μg for Aeroneb Pro compared to 1207.2 μg from Sidestream – see Table 1).

During patient use, loss of aerosol from the system, especially in position B, will be expected to be less than when in-vitro methods are used. This is due to the pressures generated by the ventilator during the inhalation and more so during the exhalation. Application of pressure would not affect the conditions in the breathing simulator, whereas the lungs of patients would obtain the effects of this due to their elasticity. Although the pressures inside the NIV tubing would be greater than *in vivo*, the results do provide a useful guide. It is important, however, that there are some in-vivo data to substantiate the in-vitro results. We have therefore designed a study to compare these two nebulisers using our urinary pharmacokinetics method in patients requiring NIV.[26] We have adapted the method for terbutaline so that minimal changes will be made to the routine management of those severely ill patients who require NIV.

Conclusions

When using NIV and inhalation/exhalation conditions akin to those used to manage COPD patients, the nebuliser should be sited between the patient and the expiration port. Although the aerodynamic characteristics from the Sidestream are slightly more favorable for lung deposition, there is a much greater fine-particle dose emitted from the Aeroneb Pro because the residual volume is much smaller. The in-vitro results suggest that 2 mg nebulised from the Aeroneb Pro would produce the same efficacy and safety as 5 mg nebulised from the Sidestream. The magnitude of this difference suggests the need to determine in-vitro data for all nebulised systems used with NIV.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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