

The Effects of Heliox on the Output and Particle-Size Distribution of Salbutamol using Jet and Vibrating Mesh Nebulisers

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ABSTRACT

There are theoretical benefits of delivering drug aerosols to patients with asthma and COPD using Heliox as a carrier gas. The objective of this study was to develop systems to allow bronchodilators nebulised by a breath enhanced jet nebuliser and a vibrating mesh nebuliser to be delivered to patients in Heliox. This was achieved by attaching a reservoir to the nebulisers to ensure inhaled Heliox was not diluted by entrained air. For the vibrating mesh nebuliser, the total output was significantly higher after 5min nebulisation when Heliox rather than air was used as the delivery gas ($p<0.001$). The proportion of drug in particles $<5\mu\text{m}$ was 58.1% for Heliox and 50.1% when air was entrained. When the breath enhanced nebuliser was used a much higher driving flow of Heliox, compared to air, was required to deliver a similar dose of drug ($p<0.05$). The total amount of drug likely to be inhaled was significantly higher when the vibrating mesh nebuliser (Aerogen) was used compared to the breath enhanced jet nebuliser (Pari LC plus) ($p<0.001$). The amount of drug likely to be inhaled was also significantly greater for the adult as opposed to paediatric breathing pattern for all nebulisers and flows tested with the exception of the Aeroneb and Heliox entrainment. In this case, total amounts were similar for both patterns but for the paediatric pattern, the time taken to reach this output was longer. Such information is required to allow appropriate interpretation of clinical trials of drug delivery using Heliox.

INTRODUCTION

Heliox is a mixture of helium and oxygen and is less dense than air. It has the advantage, due to its low density, of reducing resistance in airways with turbulent flow ⁽¹⁾. Benefits when Heliox is inhaled include improved ventilation and enhanced removal of CO₂ ^(2; 3). The properties of Heliox also make it an attractive carrier gas for drug aerosols in patients with airways obstruction to improve lung deposition ⁽⁴⁾. However, clinical trials where Heliox has been used in an attempt to improve aerosol drug delivery have produced variable results ⁽⁵⁾. Some of this variability may be explained by dilution of Heliox with air when patients inhale ⁽⁶⁾.

Jet nebulisers are driven by a pressurised gas. When a patient inhales, they will inhale drug aerosol carried in the gas used to drive the nebuliser. The patient's inhalational flow, however, is likely to be considerably higher than the flow of gas directly from the nebuliser. They will, therefore, entrain surrounding room air diluting the pressurised gas ⁽⁷⁾. If Heliox was used as the pressurised gas, the dilution from entrained room air will increase the density of the gas inhaled thereby reducing its potential benefit. To maintain the concentration of Heliox inhaled, both the gas used to run the nebuliser and the gas entrained should be Heliox. In general, studies in which a reservoir system containing Heliox was added to the nebuliser system to ensure all of the entrained air was also Heliox have shown clinical benefits such as improvements in spirometry, together with lower rates of hospital admission ⁽⁸⁻¹⁰⁾. Studies where the investigators did not describe the use of a reservoir system for Heliox have generally shown no benefit ⁽¹¹⁻¹³⁾. Interpretation of clinical trials using Heliox for nebulised drug delivery is also hindered by the lack of data on the effect of the gas on the particle size of the drug aerosol. To allow informed interpretation of drug delivery studies, detailed

information on the delivery system including the use of reservoir systems ⁽⁶⁾, particle size analysis of the drug aerosol ⁽¹⁴⁾ and the effect of breathing pattern on drug likely to be inhaled ⁽¹⁵⁾ are essential.

The aim of this study was to design and evaluate in a laboratory environment systems that allowed delivery of aerosolised drug in Heliox 21 (79% Helium and 21% Oxygen) generated by a vibrating mesh nebuliser and a conventional breath-enhanced jet nebuliser driven by Heliox. We also determined the effect of paediatric and adult breathing patterns on the amount of drug likely to be inhaled and the particle size of the aerosols produced. As the density of Heliox is significantly less than air, the impactor used was recalibrated to ensure appropriate measurements were obtained.

MATERIALS AND METHODS

Nebulisers

Nebulisers used in this study were the Pari LC Plus (Pari GmbH, Starnberg, Germany, Part No 022G8003) and the Aeroneb Professional Nebuliser System (Aeroneb Pro) from Aerogen (Ireland) Limited.

Gases

Gases used in this study were Heliox 21 (HX cylinder with integral valve), a mixture of 21% oxygen and 79% helium, from BOC. It was used with an external Heliox flow meter (Amvex

Corporation Heliox 21% oxygen, FMA 0331; calibrated from 1 – 16L/min flow) attached to the Heliox BS 6582 Schraeder outlet.

The other gas used was medical air, also from BOC. An air flowmeter (OHMEDA Serial No AKG U03143), calibrated for flows 1-15L/min, was attached to the cylinder.

A Furness Micromanometer (a sensitive pressure measuring device) and pneumotach calibrated with a 0-20L/min Rotameter (Fisher Controls Ltd, Croydon) were used for the measurement of flows.

Drug used

Salbutamol for nebulisation was Salamol (5mg/2.5ml) Steri-Neb nebuliser solution (Salbutamol sulphate nebules, Baker-Norton). Salbutamol reference standard material was Salbutamol base from GlaxoSmithKline (Product No AH3365) with a purity of 99.1% w/w (HPLC). Salbutamol was recovered from the filters and NGI stages using 75% methanol and quantified using a previously validated internal standard HPLC assay ⁽¹⁶⁾.

Matching Heliox to the patient's inhalational flow

One of the principle aims of the study was to ensure that patients would inhale Heliox that was not diluted by surrounding air.

Pari LC Plus: On inhalation from the Pari LC plus, a one-way valve opens at the top of the nebuliser allowing extra air to be entrained through the device. On exhalation, positive pressure within the nebuliser causes this valve to close. This results in additional air passing

through the nebuliser on inspiration enhancing drug delivery to the patient ⁽¹⁷⁾. To ensure the patient inhaled only Heliox 21, the top of the nebuliser was attached to a 100 litre non-diffusing gas collection bag (Hans Rudolf Inc, Canada City, Missouri, USA) filled with Heliox. This was used in conjunction with a one-way respiratory valve (patented Spiral-type diaphragm, Hans Rudolf Inc) fitted into the 35 mm bore of the bag's primary adaptor (Figure 1). The nebuliser was run using Heliox 21. For experiments where Heliox was not used, the bag was filled with air and medical air (from a cylinder) used to run the nebuliser.

Aerogen: The Aerogen produces aerosol by vibration of a mesh that is in contact with the drug solution and therefore no driving gas is required. To ensure the entire drug aerosol produced was carried in Heliox, one end of the nebuliser 'T' piece was connected to the gas reservoir bag filled with Heliox (Figure 2). When comparisons were made to delivery using air, the bag was filled with a similar amount of air.

Effect of breathing pattern on drug delivery:

The total amount of drug available for inhalation was measured using a computer controlled Pari Sinus Breathing Simulator (Pari GmbH, Starnberg, Germany). This allows simulated tidal volume, respiratory rate and respiratory time to be independently adjusted. Two different breathing patterns were used - the paediatric pattern (tidal volume of 150mL, 20 breaths per min and an inspiratory fraction of 40%) and the adult pattern (tidal volume of 600mL, 12 breaths per min and an inspiratory fraction of 40%). A Pari electrostatic filter (inspiratory) was placed in a holder via a Y-connector between the simulator and the nebuliser to capture the drug likely to be inhaled. A second filter (expiratory) was also attached to this Y-piece to allow capture of the expelled dose.

The gas reservoir bag (filled with either air or Heliox 21) was attached via the one-way valve to the top of the Pari LC Plus nebuliser and secured with nescofilm. In the case of the Aeroneb Pro nebuliser, the bag and valve were attached, via a suitable connector, to the end of the Aeroneb's T-piece.

Nebulisers were filled with the contents of a nebule (Salamol, 5mg/2.5mL). Nebulisation took place for 5min at the appropriate breathing pattern.

Studies were performed using the following combinations for both the paediatric and adult breathing patterns:

- Pari LC Plus driven by 4 and 6 L/min air, (measured by calibrated flow meter attached to the air cylinder), entraining air from reservoir bag. A flow of 6L/min was the maximum recommended for this nebuliser; higher flows result in a build-up of back pressure causing disconnection of the gas supply tubing.
- Pari LC Plus driven by 6, 12 and 15 L/min Heliox (measured by calibrated flow meter attached to Heliox cylinder), entraining Heliox from the reservoir bag. The lower density of Heliox relative to air means that higher flows of Heliox are required to produce an aerosol of similar size to that produced by the same flow of air ⁽⁶⁾.
- Aeroneb entraining air from the reservoir bag.
- Aeroneb entraining Heliox from the reservoir bag.

Pilot data for the Pari suggested that a Heliox flow of 12L/min gave a similar amount of drug in particles <5µm as seen for the same nebuliser when driven by air at 6L/min. A flow of 6L/min Heliox was chosen as a similar flow to 6L/min air for direct comparison. While

15L/min was chosen to represent a higher flow than 12L/min and an upper limit of flow, in practical terms.

Each experiment was repeated on at least four occasions. Drug deposited on the 5min inspiratory filters was recovered by dissolution into an appropriate solution and quantified by HPLC. The method of drug recovery from the filters was validated and found to be >97%. Mass balance determinations were carried out for all runs. A nebulisation time of 5min was chosen as determined from previous studies most of the drug has been nebulised within 5min and this is an acceptable time for patients to inhale from a nebuliser ⁽¹⁸⁾.

However, single experiments were also performed to determine the end of nebulisation time. This is considered to be the end of effective nebulisation. The cessation of nebulisation was taken as 1min after the beginning of sputtering ⁽¹⁹⁾. For all experiments, the amounts of drug captured on the inspiratory filters at the end of nebulisation were determined.

Particle sizing experiments:

Particle size was measured using the Next Generation Impactor (NGI, 7 stage with micro orifice collector: Model 170, MSP Corporation, Shore View, MN, USA). An external Pari electrostatic filter was present at the outlet of the impactor, as the final stage of the NGI, to collect ultra-fine particles and to protect the pump. The NGI was pre-cooled prior to each experiment to minimise evaporated losses as previously described by Berg and Asking ⁽²⁰⁾. For experiments with air, the flow through the NGI was set at 15 L/min ⁽²¹⁾.

Effective cut-off diameters (ECD) for the impactor stages have already been determined for air at 15 L/min (Marple et al, 2004) to allow use of this impactor with nebuliser systems. The impactor was recalibrated for the use of Heliox using the equation from Newton ⁽²²⁾. Cut-offs were calculated for each stage of the NGI for Heliox at a flow of 15 L/min through

the impactor, ie: $ECD (\mu m) = 1.233 \times 10^4 (N\eta W^3/Q)^{1/2}$ where ECD is the effective cut-off diameter, N is the number of jet stages, η is the gas viscosity, W is the diameter of the stage jets and Q is the gas flow.

Table 1 summarises the calculations of the ECDs for Heliox. For comparison, the ECDs for air are also included.

These cut-offs for Heliox were 18.79, 9.17, 5.50, 3.32, 2.03, 1.27 and 0.82 μm for stages 1-7, respectively.

To set the flow of Heliox at 15L/min through the impactor the following method was employed. Output from the calibrated flow meter attached to the Heliox 21 cylinder was directly connected to the Furness Micromanometer via a pneumotach. A flow of 15L/min produced a specific reading on the Micromanometer that was recorded. Experiments were set-up with the pneumotach in place and with a reservoir bag (full of Heliox) attached. The vacuum pump attached to the end of the NGI was switched on and adjusted until the reading on the Micromanometer was equivalent to a Heliox flow of 15L/min.

The top of the Pari nebuliser was again attached to the reservoir bag filled with either air or Heliox to ensure no dilution with surrounding room air. In all cases, the driving gas matched the gas in the reservoir bag. For the Aerogen, the reservoir was connected to the T- piece.

For particle sizing experiments nebulisation time was 3 minutes in all cases and quadruplicate measurements were made. Salbutamol was recovered from all stages of the NGI and external filter using methanol as a solvent and quantified by HPLC. The amount of drug contained in particles <3 μm and <5 μm was calculated. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were also determined.

In our experiments, the mass of drug collecting in the throat and depositing on the first stage of the NGI were not included in the determination of aerosol properties, such as, MMAD and GSD. However, the drug collecting in these components was considered for the purpose of characterising the total cloud from the nebuliser, i.e.: when calculating the amount and percentage of drug in particles $<6\mu\text{m}$, $<5\mu\text{m}$ and $<3\mu\text{m}$.

Combining the total output of drug at 5min from the breathing simulation analyses with the particle-sizing data (% particles $<5\mu\text{m}$ and $<3\mu\text{m}$) allowed the estimation of the amount of drug likely to be inhaled that is contained within various particle size fractions.

Statistical Analysis:

A series of two-way ANOVAs with Bonferroni post-tests were performed on the breathing simulation data and on the results for the amount of drug (μg) in particles $<5\mu\text{m}$. A series of one-way ANOVAs were performed on the percentage of drug in particles $<5\mu\text{m}$.

RESULTS:

Figures 3 and 4 show the total outputs to the breathing simulator filter after 5min nebulisation for the adult and paediatric breathing patterns, respectively, and the amounts of salbutamol calculated from our results to be in particles $<5\mu\text{m}$ and $<3\mu\text{m}$.

Results for the amounts of drug captured on the inspiratory filters (representing the total amount of drug available for inhalation) after 5min and at the end of nebulisation, together with the times to dryness, are shown in Table 2 for both breathing patterns.

In all experiments, output with the adult breathing pattern was significantly higher ($p < 0.0001$) than with the paediatric pattern, with the exception of the Aeroneb and Heliox entrainment. In this case, total amounts were similar for both patterns but for the paediatric pattern, the time taken to reach this output was longer.

Using the Pari with air at 4 and 6L/min, the total outputs and amounts of drug in particles $< 5\mu\text{m}$ were similar ($p > 0.05$).

Using the Pari with Heliox at 12 or 15L/min gave a higher total output with the adult breathing pattern ($p < 0.05$) compared to 6L/min. The proportion of drug in particles $< 5\mu\text{m}$ increased with higher flows for both breathing patterns ($p < 0.001$).

Using the Aeroneb with entrained Heliox resulted in higher total drug output after 5min nebulisation compared to when air was entrained ($p < 0.001$). For the Aeroneb with entrained air, 50.1% of the aerosol cloud contained drug in particles $< 5\mu\text{m}$. When Heliox was the entrainment gas, this proportion increased to 58.1%.

Total drug outputs for the Aeroneb for both breathing patterns were significantly higher as compared to the Pari after 5min nebulisation ($p < 0.001$). These differences were maintained until the end of effective nebulisation.

The amounts of drug calculated to be in particles $<5\mu\text{m}$ were significantly higher for the Aeroneb with Heliox entrainment, for both breathing patterns, as compared to all other combinations ($p<0.001$).

MMADs for the Pari at flows of 4 and 6 L/min of air were $3.8 \pm 0.16 \mu\text{m}$ (Mean \pm S.D.) and $2.9 \pm 0.18 \mu\text{m}$ respectively. For the Aeroneb with air entrainment the MMAD was $4.5 \pm 0.13 \mu\text{m}$. MMADs for the Pari at flows of 6, 12 and 15 L/min with Heliox as driving gas were $3.62 \pm 0.08\mu\text{m}$, $1.7 \pm 0.18\mu\text{m}$ and $1.47 \pm 0.3\mu\text{m}$ respectively. For the Aeroneb with Heliox entrainment, the MMAD was $3.99 \pm 0.12 \mu\text{m}$.

DISCUSSION

In this study, we designed and evaluated laboratory based systems that allowed delivery of a nebulised bronchodilator in Heliox, undiluted by the surrounding air. .

We studied two different types of nebuliser. The Pari LC Plus is a breath-enhanced nebuliser that is commonly used in a home and hospital setting for the delivery of aerosolised medications to patients. By attaching a reservoir of Heliox to the top of the nebuliser, entrained gas and thus all gas likely to be inhaled was Heliox. The vibrating mesh nebuliser was chosen due to the lack of need for a driving gas. The reservoir containing Heliox was attached to the T-piece of the device ensuring all gas likely to be inhaled was Heliox. Using these systems with a breathing simulator, replicating an adult and paediatric breathing pattern, we were able to determine the amount of drug likely to be inhaled with these breathing patterns. The drug likely to be inhaled was determined by assaying filters placed between the nebuliser and the breathing replicator. It must be remembered that this is a

laboratory estimate of the total dose inhaled and does not necessarily represent the dose reaching the lower respiratory tract. We found Heliox significantly affected the amount of drug likely to be inhaled, compared to air, from both devices. For the Aeroneb vibrating mesh nebuliser the total output was significantly higher when Heliox rather than air was used as the delivery gas. We speculate that Heliox causes less internal losses within the drug delivery devices. When the breath-enhanced nebuliser was used, a much higher driving flow of Heliox, compared to air, was required to deliver a similar dose of drug.

Our results concentrate on the output of drug in the first 5min of nebulisation. From previous work, the majority of nebulisation takes place in 5min and this is also considered an acceptable time for the patient to breathe from a nebuliser ⁽¹⁸⁾. We also report on the amount of drug released at the end of effective nebulisation. The proportions of drug released at the end of effective nebulisation did not differ significantly from those at 5min. The main exception was the Aeroneb with Heliox entrainment for the adult breathing pattern. In this case, the majority of drug was delivered within 5min. When the Aeroneb and air entrainment were used with the same breathing pattern, drug continued to be released for a further 2min. As expected, the amount of drug inhaled for the adult breathing pattern was significantly greater than when the paediatric pattern was used. The only exception was the Aeroneb when used with entrained Heliox. In this case, the total amount delivered for a paediatric breath pattern was similar for an adult breath simulation, although the time taken to reach this output was longer. These results confirm the importance of breathing pattern to determine drug delivery from nebulisers ⁽²³⁾.

The use of a reservoir system, ensuring Heliox inhaled by a patient is not diluted by entrained air, appears crucial to its effectiveness as a carrier gas for bronchodilator aerosols ⁽⁶⁾. It has been hypothesised that the lower density of Heliox would result in less turbulent flow and, thus, improve drug delivery to the lungs in patients with airways obstruction. Dilution of the Heliox by air would increase the density of the gas inhaled and, if dilution was significant, negate the potentially beneficial effects of Heliox. Studies in adults with stable asthma ⁽⁹⁾ and during exacerbations ⁽⁸⁾, where a reservoir of Heliox was used, ensuring no dilution of the gas, showed improvements in lung function compared to air. Use of a reservoir system for Heliox also showed benefits in a paediatric emergency room study in terms of early discharge and patient symptom scores ⁽¹⁰⁾. Studies where patients entrained surrounding room air that diluted the Heliox used to drive the nebuliser, have generally failed to show benefit ⁽¹¹⁻¹³⁾.

For effective therapy, it is also crucial that the aerosolised drug be contained in particles that are likely to reach the lower respiratory tract ⁽¹⁵⁾. We were surprised, therefore, that the majority of clinical studies evaluating nebulisation with Heliox failed to study its effect on aerosol particle size. To evaluate particle size we used the Next Generation Impactor. This impactor has been calibrated at flows of both 15 and 30 litres/minute ⁽²¹⁾, the former chosen as the optimal flow for assessment of the particle size distribution from nebulisers. As flow through an impactor depends on the density of the gas, recalibration is required if a different gas is used. In this study we used an impactor flow of 15L/minute and calculated the cut-off diameters for the individual stages of the impactor using the equation derived by Newton and colleagues ⁽²²⁾. In the one clinical study where particle size was measured, there is no mention of calibration of the impactor used to cater for the lower density of Heliox.

When jet nebulisers are used the lower density of Heliox relative to air means that higher flows of Heliox are required to produce an aerosol of similar size to that produced by the same flow of air ^(24, 25). Our results support these findings with significantly less salbutamol available for inhalation in small particles ($<5\mu\text{m}$) when the Pari jet nebuliser was run by Heliox at 6L/min compared to air at the same flow. Increasing the flow to 12L/min Heliox increased output of drug in small particles towards that of the Pari jet nebuliser run using air at 6L/min. There was no advantage of using a higher flow of Heliox of 15L/min. Total output of drug was also significantly less at the lowest flow of Heliox (6L/min) compared to a similar flow of air.

As expected, an increase in Heliox flow with the Pari resulted in a decrease in the MMAD of the aerosol, from $3.6\mu\text{m}$ at 6L/min to $1.7\mu\text{m}$ at 15L/min. From our results, a flow of 6L/min of Heliox for the Pari is clearly not optimal in terms of total drug output and particle-size distribution. As expected, the MMAD when Heliox was used to drive the Pari was greater than when air was used at the same flow. This is consistent with the results of Corcoran and co-workers ⁽²⁴⁾. They used a Hudson Micromist nebuliser run with air at 8L/min and Heliox(70/30) at 8L/min using saline sprays and found a higher MMAD ($4.3\mu\text{m}$) for Heliox compared to $3.8\mu\text{m}$ for air. Testing the Pari at high flows of air equivalent to those of Heliox was not possible due to practical limitations.

Our results differ from a study by Hess and colleagues ⁽¹⁾ who found increasing the flow of Heliox use to drive the nebuliser resulted in an increase in the particle size (MMAD) of the drug aerosol. The reasons for this are not clear as, in general, increasing the driving flow through a nebuliser usually results in a smaller particle-size. If the flow is too high, spitting of large particles may occur which could affect the particle-size distribution analysis.

Another factor was the lack of a reservoir of Heliox in their study. They determined aerosol

particle-size using an 11- stage cascade impactor at a flow of 2 litres/minute that was recalibrated for Heliox.

Our results give an estimate of the effect of Heliox on the likely dose of drug inhaled and the amount contained in particles likely to reach the lung. Such information is crucial to plan clinical studies and to allow appropriate interpretation of clinical studies. The effect of nebuliser choice in this study resulted in approximately twice the dose of drug inhaled using the vibrating mesh nebuliser despite a similar nominal dose being ‘prescribed’. Other studies have shown that depending on the nebuliser chosen the amount of drug delivered to a patient may vary five fold ⁽¹⁵⁾.

The use of Heliox at the same inhalational flow as air would be predicted to result in less turbulent flow in the upper airways and if the drug aerosol in each carrier gas was the same, greater lung deposition. However, the inhalation of Heliox by patients will result in an increased inhalational flow and tidal volume ^(2; 3) due to the lower density of the gas. These studies ^(2; 3), however, relate to exercise physiology and their applicability to aerosol drug delivery is speculative. This makes predictions of deposition in the upper airway more difficult. As argued by Corcoran and Gamard, the increased respiratory rate associated with inhalation with Heliox may reduce the settling time for these particles. However, the larger tidal volumes breathed when Heliox is inhaled combined with less momentum loss in the upper airway is likely to deliver drug aerosols deeper into the lung ⁽⁶⁾. In our study, we found a significantly greater dose of drug was available for inhalation when the vibrating mesh nebuliser was used with Heliox compared to air. Thus if clinical benefit was found when Heliox was used, this could be simply due to a greater amount of drug being inhaled. Any

additional effect due to the properties of Heliox carrying the drug into the lung would be difficult to determine. The methodology we have developed will help us to design a study to determine the effect of Heliox as a carrier gas once the drug aerosol has been inhaled. For example, using the vibrating mesh nebuliser we can alter the dose of drug so that the same amount of drug is inhaled when either Heliox or air is used. This will allow us to tease out whether Heliox as a carrier gas improves lung deposition of drug in patients with airways obstruction and if this is associated with clinical benefit.

In summary, we have developed and evaluated systems in the laboratory to allow the delivery of nebulised bronchodilators in undiluted Heliox. These systems could be adapted for use with patients, to allow the concentration of Heliox inhaled to be constant and not diluted by surrounding room air. Maintaining the concentration of Heliox is an essential component to improving enhanced delivery of drug to the lung. We have shown that the use of Heliox has a significant effect on the total amount of bronchodilator likely to be inhaled and also the amount of the drug contained in particles that are likely to reach the lower respiratory tract. Such information is required to help interpret clinical trials of drug delivery using Heliox.

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Table 1. Calculation of Effective Cut-off Diameters (ECDs) for Heliox21 at a flow of 15L/min through the Next Generation Impactor.

| NGI Stage Number | Standard ECDs (μm) at 15L/min for Air | Number of jets (N) | Diameter (cm) of Stage Jets (W) | Gas viscosity (poise) of Heliox21 (η) | Gas flow (cm ³ /sec) of Heliox21 (Q) | Calculated ECDs (μm) for Heliox21 at 15L/min |
|------------------|---------------------------------------|--------------------|---------------------------------|---------------------------------------|---|--|
| 1 | 14.10 | 1 | 1.43 | 1.9847×10^{-4} | 250 | 18.79 |
| 2 | 8.61 | 6 | 0.488 | 1.9847×10^{-4} | 250 | 9.17 |
| 3 | 5.39 | 24 | 0.219 | 1.9847×10^{-4} | 250 | 5.50 |
| 4 | 3.30 | 52 | 0.1207 | 1.9847×10^{-4} | 250 | 3.32 |
| 5 | 2.08 | 152 | 0.0608 | 1.9847×10^{-4} | 250 | 2.03 |
| 6 | 1.36 | 396 | 0.0323 | 1.9847×10^{-4} | 250 | 1.27 |
| 7 | 0.98 | 630 | 0.0206 | 1.9847×10^{-4} | 250 | 0.82 |

| | | | | | | | |
|---|--------------------------|------------|----------------------------------|----------------|----------------|---------------|------------------|
| Table 2. Amounts (mcg) of Salbutamol captured on inspiratory filters after 5min nebulisation and at the end of nebulisation from the Pari LC Plus and Aeroneb Pro nebulisers for adult and paediatric simulated breathing patterns. | | | | | | | |
| | PARI LC+ | PARI LC+ | PARI LC+ | PARI LC+ | PARI LC+ | AERONEB | AERONEB |
| | 4L/min AIR | 6L/min AIR | 6L/min HELIOX | 12L/min HELIOX | 15L/min HELIOX | Entrained AIR | Entrained HELIOX |
| | (<---Entrained AIR---->) | | (<-----Entrained HELIOX ----->) | | | | |
| ADULT BREATHING PATTERN | | | | | | | |
| Amount of drug on insp. filter after 5min (mcg) | 935 (54.4) | 889 (36.3) | 599 (46.9) | 796 (106) | 768 (85.7) | 1630 (127) | 1997 (180) |
| Time to end of nebulisation (min) | 7.0 | 6.0 | 10.25 | 7.0 | 7.25 | 7.0 | 6.0 |
| Amount of drug on insp. filter at end of nebn (mcg) | 987 | 1166 | 872 | 906 | 827 | 2005 | 2037 |
| PAEDIATRIC BREATHING PATTERN | | | | | | | |
| Amount of drug on insp. filter after 5min (mcg) | 493 (70.1) | 513 (33.8) | 343 (23.3) | 396 (51.8) | 357 (74.4) | 1206 (54.7) | 1555 (136) |
| Time to end of nebulisation (min) | 12.0 | 8.25 | 14.75 | 7.25 | 7.0 | 6.5 | 7.0 |
| Amount of drug on insp. filter at end of nebn (mcg) | 693 | 562 | 721 | 460 | 332 | 1442 | 1958 |
| (Means & 95% C.I. n=4, for drug amounts on inspiratory filters at 5min; single determinations for the end of nebulisation time and amounts of drug on inspiratory filters at the end of nebulisation.) | | | | | | | |
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Reprint Requests

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