TECHNICAL NOTE

Efficient drug delivery to the lungs from a continuously operated open-vent nebulizer and low pressure compressor system


ABSTRACT: A comparison of aerosol delivery has been made between two open-vent Pari jet nebulizers. Intermittent and continuous delivery were compared for one of the nebulizers.

Ten healthy volunteers inhaled 99mTc-labelled diethylenetriamine penta-acetic acid (DTPA) aerosols on three occasions.  The Pari LC device was operated both intermittently (by a manual interrupter that generated aerosol only in synchrony with inhalation) and continuously.  The Pari LL nebulizer was operated only in the intermittent mode.  A system of inspiratory and expiratory valves was fitted to each nebulizer in order to direct airflow.  Both nebulizers were powered by Pari Boy compressors.

The mean (SD) whole lung deposition for the LL nebulizer was 11.1 (4.0)% of the nominal dose, compared to 15.3 (12.8)% and 12.8 (7.9)% for the LC used with intermittent and continuous operation, respectively.  These differences were not statistically significant.  Regional deposition patterns within the lungs were similar for the three nebulizer systems.

These data show that efficient nebulizer systems using relatively low power compressors are possible, and suggest that continuously operated open-vent nebulizers may be designed to give lung deposition comparable to that achieved by nebulizers fitted with manual interrupters.

Eur Respir J., 1994, 7, 1177–1181.


Correspondence: S.P. Newman
Pharmaceutical Profiles Ltd
2 Faraday Building
Highfields Science Park
University Boulevard
Nottingham NG7 2QP
UK

Keywords: Bronchodilator inhalation therapy nebulizer

Received: August 23 1993
Accepted after revision January 18 1994

The study was funded by Paul Ritzau Pari-Werk GmbH.

Nebulizers fulfil a number of important roles in inhalation therapy.  They are widely-used for bronchodilator therapy in patients with asthma and bronchitis, and may be used to deliver larger doses than can be conveniently given by pressurized metered-dose inhaler or by powder inhaler [1].  Patients unable to use a pressurized metered-dose inhaler correctly may be treated using a nebulizer for delivery, since relaxed tidal breathing is used to inhale the drug aerosol, rather than a very precise inhalation manoeuvre that may be difficult to perform correctly [2].  Nebulizers are very versatile devices, that can be used to deliver virtually any drug formulated as a solution or as a micronized suspension, and in doses exceeding 100 mg for some drug substances [3, 4].

It is clear, however, that there are wide differences in the performance of nebulizers between models, reflected in a wide range of droplet size distributions and drug outputs [5, 6], and in the percentage of the drug delivered to the lungs [7–11].  The drug delivery characteristics of any nebulizer cannot be inferred from those of another model, and must be determined separately.  In this study, we have assessed the performance of a new LC jet nebulizer system (Pari-Werk GmbH) by gamma scintigraphy, and have compared it with an existing system, namely the Pari LL Long-Life nebulizer (Pari-Werk GmbH).

It has been assumed [2] that nebulizers which operate continuously are less efficient than those in which the aerosol generation is intermittent (i.e. synchronized with inhalation by the patient using a manual interrupter).  In order to avoid the inconvenience of a manual interrupter, and yet to reduce wastage of aerosol during continuous nebulization, an open-vent system, incorporating inhalation and exhalation valves, has been developed.  The inhaled air is drawn through a ventilation tube past the point of aerosol generation (fig. 1).  This system allows for enhanced generation of aerosol during the inspiration phase of breathing and reduced release of aerosol during the expiration phase.  This effect has been demonstrated in vitro [12], but has yet to be proved in vivo.  We have, therefore, assessed aerosol deposition from the LC nebulizer using both continuous and intermittent aerosol delivery.
Methods

Nebulizer systems

The three nebulizer systems were powered by Pari Boy compressors, and were as follows: 1) Pari LL nebulizer, with manual interrupter for intermittent delivery; 2) Pari LC nebulizer, with manual interrupter for intermittent delivery; and 3) Pari LC nebulizer, with continuous delivery.

A system of inspiratory and expiratory valves was fitted to each nebulizer in order to direct airflow, arranged in such a way that droplet sizes and aerosol outputs were not affected (fig. 1). Operating characteristics and droplet size distributions for each nebulizer system are shown in table 1. Droplet size distributions were determined by Malvern Instruments series 2600 laser analyser [13], operating at 20°C and 45% relative humidity, under steady-state conditions, with a simulated inhalation flow of 20 l·min⁻¹. The operating pressure and nebulizer gas flow are, respectively, the pressure upstream of, and flow through, the nebulizer during operation. When used in the continuous mode, pressures and flows were set at lower values in order to give a standardized nebulization time to "dryness" for each system. Each nebulizer was fitted with a mouthpiece and with an exhalation filter, to trap both exhaled aerosol and (for continuous delivery) aerosol blown out of the nebulizer during the exhalation phase of breathing. Each subject used a different individual nebulizer unit, but only a single compressor unit was used with each type of nebulizer.

Subjects studied

Ten healthy volunteers (age range 20–58 yrs; one male and nine females) took part in the study. All were non-smokers of at least 12 months duration, and none of the volunteers had any clinically significant abnormal haematology or clinical chemistry results, when tested within 21 days of entry to the study. On entry to the study, forced expiratory volume in one second (FEV₁) ranged 90–115% predicted [14]. Each volunteer gave informed written consent in the presence of a witness, and the study was approved by the Quorn Research Review Committee, Leicestershire, UK. Administration of the radioactive aerosol was approved by the Department of Health, London, UK. The results of previous studies have shown that with 10 subjects having 15% of the aerosol dose deposited in the lungs, it is possible to detect a difference of 5% of the dose with a power of 80% [15].

Protocol

Each volunteer performed three inhalation studies in a randomized order, at least 24 h apart. The nebulizers were filled with 3 ml of ⁹⁹ᵐTc labelled diethylenetriamine penta-acetic acid (DTPA) solution, containing 30 MBq ⁹⁹ᵐTc. The volunteers were instructed to inhale from the nebulizers by relaxed tidal breathing for 15 min, in order to ensure maximum delivery of the placebo solution. For intermittent aerosol delivery, the volunteers operated the manual interrupter on the side of the nebulizer to coincide with the inhalation phase of breathing. The subjects were instructed to press the interrupter immediately prior to the start of an inhalation, and to release the interrupter immediately after the end of an inhalation. They were observed throughout the administration procedure, in order to ensure compliance with these instructions. In order to prevent any loss of aerosol via the nose, cotton wool plugs were inserted into the nostrils and held in place with surgical tape throughout the administration procedure.

The following scans were taken by a General Electric Maxi camera, connected to a Bartec data processing system, upon which each image was stored as a 128 by 128 matrix of picture elements: 1) the nebulizer, before administration of the ⁹⁹ᵐTc-labelled aerosol; 2) posterior
view of the lungs immediately after administration; 3) anterior view of the lungs immediately after administration; 4) lateral view of the upper airways (mouth and oropharynx) immediately after administration; and 5) the nebulizer, exhalation filter and nose-plugs after administration.

All counts were corrected for radioactive background, and, where appropriate, for radioactive decay of 99mTc. The percentage of the dose retained in the nebulizer, and deposited on the exhalation filter and nose-plugs was determined by comparison with the count rate from the nebulizer before administration. The remainder of the dose was assumed to be in the body, and was divided into lung and upper airway fractions, expressed as percentages of the amount initially placed in the nebulizer. Radioactivity detected in the stomach was assumed to have been deposited in the upper airways. The geometric means of the posterior and anterior lung and stomach count rates were calculated, and the data were corrected for tissue attenuation of gamma rays, using the equations of Flemming [16], following the measurement with calipers of each individual subject's body thickness.

On one study day, each volunteer inhaled 81mKr gas from a radionuclide generator, and a posterior ventilation scan was performed in order to give an outline of the lungs. This outline was used to divide the aerosol views of the lungs into central, intermediate and peripheral zones, as described previously [17, 18]. The ratio of peripheral to central zone deposition was calculated.

FEV1 was measured prior to aerosol administration on each study day, and at least 30 min after administration of the radioaerosol, in order to check that no bronchoconstriction had occurred.

The scintigraphic data were analysed by the Wilcoxon matched-pairs signed-ranks test [19], in order to look for significant differences in the deposition patterns between treatment regimens. A p-value of ≤0.05 was taken to indicate statistical significance.

**Results**

The fractionation of the dose between lungs, upper airways, nebulizer body and exhaled air filter is shown in table 2, and was similar for each of the three systems. There was a trend towards a greater lung deposition for the LC device operated intermittently, but this was not statistically significant. There was considerable inter-subject variability in deposition for each nebulizer (table 3). Similar percentages of the dose (means 25, 26 and 27%) were deposited in the body from the three devices, and similar percentages of the dose were retained in the nebulizer (means 62, 62 and 57%). The percentage of the dose retained on the exhaled air filter was significantly greater for the LC operated continuously than for the other two systems (p<0.05 compared to LL nebulizer; p<0.01 compared to LC nebulizer operated intermittently). Aerosol collected on the filter averaged 35 and 32% of the amount nebulized for LL and LC nebulizers operated intermittently, and 38% of the amount nebulized for the LC nebulizer operated continuously.

The deposition patterns within the lungs were similar for the three nebulizer systems (table 4). There was a trend towards greater deposition in each of central, intermediate and peripheral zones for the LC system operated intermittently, but this was not statistically significant. Mean (SD) FEV1 values were 3.19 (0.36) l before aerosol administration, and 3.18 (0.38) l when measured 30 min afterwards.

**Table 2.** Percentages of the nominal dose deposited in the lungs and upper airways, or retained in the nebulizer and filter, for Pari LL nebulizer and the LC nebulizer operated intermittently and continuously.

<table>
<thead>
<tr>
<th>Deposition site</th>
<th>Amount deposited/retained % nominal dose</th>
<th>Pari LL intermittent</th>
<th>Pari LC intermittent</th>
<th>Pari LC continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung</td>
<td></td>
<td>11.1 (4.0)</td>
<td>15.3 (12.8)</td>
<td>12.8 (7.9)</td>
</tr>
<tr>
<td>Upper airways</td>
<td></td>
<td>13.8 (5.1)</td>
<td>10.9 (6.5)</td>
<td>14.2 (7.8)</td>
</tr>
<tr>
<td>Nebulizer</td>
<td></td>
<td>61.9 (6.2)</td>
<td>61.5 (16.0)</td>
<td>56.8 (13.1)</td>
</tr>
<tr>
<td>Filter†</td>
<td></td>
<td>13.2 (3.0)</td>
<td>12.2 (3.4)</td>
<td>16.2 (2.7)</td>
</tr>
</tbody>
</table>

Data are presented as mean, and so in parenthesis. *: p<0.05 compared to Pari LL; †: p<0.01 compared to Pari LC intermittent; ‡: including cotton-wool nose-plugs.

**Table 3.** Individual whole lung deposition data (percentage of nominal dose) from three nebulizer systems.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Pari LL intermittent</th>
<th>Pari LC intermittent</th>
<th>Pari LC continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.5</td>
<td>41.8</td>
<td>32.2</td>
</tr>
<tr>
<td>2</td>
<td>6.7</td>
<td>9.4</td>
<td>6.4</td>
</tr>
<tr>
<td>3</td>
<td>10.7</td>
<td>7.9</td>
<td>8.8</td>
</tr>
<tr>
<td>4</td>
<td>3.8</td>
<td>4.4</td>
<td>20.2</td>
</tr>
<tr>
<td>5</td>
<td>13.0</td>
<td>5.1</td>
<td>11.5</td>
</tr>
<tr>
<td>6</td>
<td>13.3</td>
<td>12.9</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>11.2</td>
<td>11.2</td>
<td>13.3</td>
</tr>
<tr>
<td>8</td>
<td>15.5</td>
<td>23.9</td>
<td>10.5</td>
</tr>
<tr>
<td>9</td>
<td>9.0</td>
<td>31.3</td>
<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>10.2</td>
<td>5.2</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Mean 11.1 15.3 12.8

**Table 4.** Regional deposition patterns within the lungs.

<table>
<thead>
<tr>
<th>Regional lung deposition</th>
<th>Pari LL intermittent</th>
<th>Pari LC intermittent</th>
<th>Pari LC continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central zone (%)</td>
<td>3.3 (1.3)</td>
<td>4.7 (4.1)</td>
<td>3.7 (2.8)</td>
</tr>
<tr>
<td>Intermediate zone (%)</td>
<td>3.5 (1.2)</td>
<td>4.6 (3.6)</td>
<td>3.9 (2.2)</td>
</tr>
<tr>
<td>Peripheral zone (%)</td>
<td>4.2 (1.7)</td>
<td>6.1 (5.1)</td>
<td>5.1 (3.1)</td>
</tr>
<tr>
<td>Peripher: central zone ratio</td>
<td>1.3 (0.3)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.2)</td>
</tr>
</tbody>
</table>

Data are presented as mean, and so in parenthesis.
Discussion

The scintigraphic data in the present study have shown that nebulizer systems can be efficient when using relatively weak compressors, generating in-line pressures <100 kPa, and flow through nebulizers below 4 l/min⁻¹. Low-flow, low-pressure compressors have several advantages for inhalation therapy, namely lighter-weight components, quieter operation, less vibration, better durability, and less power consumption.

Previous studies of drug delivery from nebulizers have shown wide variability between different nebulizer systems [7–11]. One of these studies has shown a tenfold variation in the percentage of the drug dose delivered to the lungs (2–19%) between the most and least efficient of the nebulizer systems tested [11]. This variability, in part, reflects the droplet size distributions, drug output rates generated by different nebulizers, but is also related to the characteristics of the compressor or to the gas flow through the nebulizer. Nebulizer systems incorporating powerful compressors that generate relatively high gas flows through nebulizers (>8 l/min⁻¹) have been shown to enhance drug delivery to the lungs [8, 17].

The compressors used in the present study generated flows and pressures at the lower end of the ranges for different compressor systems [20], but nevertheless produced an efficient drug delivery. The chosen treatment time of 15 min was long enough to ensure nebulization to "dryness" and maximum aerosol output using a 3 ml volume fill.

The whole lung deposition data resembled those previously observed for the Pari Boy 37.80 nebulizer (13% lung deposition) which was operated intermittently [11]. We have used a solution volume of 3 ml in the present study; a further improvement in deposition might be achieved by using a larger solution volume [21], but this would occur at the expense of increasing the nebulization time. Longer treatment times might also be required for very viscous antibiotic solutions [5], but the delivery of these substances was outside the scope of the study. Commercially available drug ampoules contain 2–2.5 ml of solution; it is likely that the nebulization of these volumes would result in slightly reduced efficiency but shorter treatment times than those observed in this study.

There was considerable variability in lung deposition, both between and within subjects. Factors contributing to variability include radioactive statistical counting errors and variations in nebulizer output [22]. However, we consider it unlikely that these two factors contributed significantly, since we collected at least 2×10⁴ counts from the lungs in all studies, and the variation in performance between individual nebulizer and compressor units was small, as shown in table 1. Variability in deposition would have been increased by using inappropriate tissue attenuation correction factors, but an individual correction was made for each subject, as recommended by Messina and Smaldone [23]. It is likely that variability in deposition would have been reduced in the present study, had we controlled the subjects' breathing rates and tidal volumes [24]. However, we chose to allow the subjects to breathe spontaneously, in order to reflect more accurately the delivery of aerosol in clinical practice. It is important to note that variability in lung deposition between subjects is a common and expected feature of studies of this nature [22, 25], and, in part, reflects random variability between subjects in airway anatomy and airflow patterns [26].

Our data suggest that it is possible to improve the performance of specific low-flow, low-pressure, nebulizers equipped with open vents, to the point where they give comparable deposition data to those seen from nebulizers fitted with manual interrupters. When a nebulizer operates continuously, aerosol generated during the exhalation phase of breathing cannot reach the subject, and will be blown out through the exhalation port. On theoretical grounds, a nebulizer operating continuously is expected to have a substantially worse drug delivery than the same nebulizer operating intermittently (the generation of aerosol being synchronized with inhalation). Since inhalation occupies less than half of the breathing cycle, the majority of the aerosol generated should be wasted during continuous nebulization, and deposited on the filter. For intermittently operated nebulizers, the amount of aerosol collected on the filter can be assumed to consist mainly of the exhaled aerosol fraction. However, the fraction collected on the filter averaged 35 and 32%, respectively, of the amount nebulized for LL and LC nebulizers operated intermittently, and was only slightly increased to 38% by using the LC nebulizer without the manual interrupter, suggesting that only a minimal wastage of aerosol is produced in the exhalation phase. This effect is probably a feature of open-vent nebulizers equipped with a valve system, resulting in nearly the same lung deposition as that with intermittent aerosol delivery. However, this finding may be device-specific, and other results could have been obtained with other nebulizer models. By contrast, conventional nebulizers, in which the inhaled air is not drawn past the spray nozzle, function in a different manner, and there is a substantial increase in aerosol waste trapped on the exhalation filter during continuous operation [11].

Although the LC without the manual interrupter was operated at a lower flow rate (3.0 l/min⁻¹) and in-line pressure (49.4 kPa) than the LL and LC operated with the interrupter (ca 3.6 l-min⁻¹ and ca 70 kPa), its efficiency was similar. This might permit the future development of new, small, and light-weight, portable compressor units. These studies were conducted in healthy subjects, and it is possible that different results would have been observed in asthmatic patients with severe airways obstruction. However, nebulizers can be used to deliver a very wide range of drug substances for a variety of indications, and, for patients with little or no airways obstruction, these data would be applicable.

References

Respir Care 1991; 36: 939–951.
3. Hodson ME, Penketh ARL, Batten JC. Aerosol car-
benicillin and gentamicin treatment of pseudomonas infec-
tion in patients with cystic fibrosis. 
penicillin as sole therapy for 
Pneumocystis carinii pneu-
monia in patients with acquired immunity deficiency syn-
drome. 
5. Newman SP, Pellow PGD, Clay MM, Clarke SW. – 
Evaluation of jet nebulisers for use with gentamicin solu-
tion. 
6. Sterk PJ, Plomp A, Van der Vate JF, Quanjer PH. 
Physical properties of aerosols produced by several jet 
and ultrasonic nebulizers. 
7. Matthys H, Köhler D. Pulmonary deposition of aerosols 
different mechanical devices. 
9. Ilowite JS, Baskin MI, Sheetz MS, Abd AG. Delivered dose and regional distribution of aerosolised pentami-
dine using different delivery systems. 
10. Thomas SHL, O'Doherty MJ, Page CJ, Nunan TO, Bateman NT. Which apparatus for inhaled pentamidine? A comparison of pulmonary deposition via eight nebu-
lizers. 
11. Hardy JG, Newman SP, Knoch M. Lung deposition from four nebulizers. 
12. Knoch M, Wunderlich E, Geldner S. A nebulizer sys-
tem for highly reproducible aerosol delivery. 
J Aerosol Med 1993; 9 (Suppl.); 73.
14. Quanjer PH. Standardised lung function testing. 
15. Newman SP, Clark AR, Talae N, Clarke SW. Pressur-
ised aerosol deposition in the human lung with and without an “open” spacer device. 
16. Fleming JS. A technique for the absolute measurement of activity using a gamma camera and computer. 
17. Newman SP, Woodman G, Clarke SW. Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebu-
lizer system and breathing pattern. 
18. Agnew JE, Bateman JRM, Pavia D, Clarke SW. Radio-
uclide demonstration of ventilatory abnormalities in mild asthma. 
20. Newman SP, Pellow PGD, Clarke SW. The flow-pres-
sure characteristics of compressors used for inhalation therapy. 
Eur J Respir Dis 1987; 71: 122–126.
21. O'Doherty M, Thomas S, Page C, Badbeer C, Nunan T, Bateman N. Pulmonary deposition of nebulised pentami-
dine isethionate: effect of nebulizer type, dose and volume of fill. 
23. Messina MS, Smaldone GC. Evaluation of quantitative aerosol techniques for use in bronchoprovocation tests. 
24. Ilowite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. 
25. Borgström L, Newman SP. Total and regional lung deposition of terbutaline sulphate inhaled via a pressurised MDI or via Turbuhaler. 