Delivered Dose Comparison between Breath-activated (Metered Dose and Non-metered Dose) and Breath-enhanced Nebulizers

RHM Hatley, S Byrne, B Woodington

Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester, West Sussex, PO20 2FT, UK

Summary

In previous studies we have looked at the variability in dose between venturi jet, breath-enhanced, and mesh nebulizers. 1,2 In this study we extended the investigation to cover breath-activated nebulizers, comparing them to a representative breath-enhanced nebulizer. Here we report on a comparison of the delivered dose (DD) from the AeroEclipse II (AeroEclipse II; Monaghan Medical Corp.), a non-metered breath-activated nebulizer, the I-neb Adaptive Aerosol Delivery (AAD) System (Respironics Respiratory Drug Delivery (UK) Ltd), a metered breath-activated nebulizer, and the LC Sprint (PARI GmbH), a breath-enhanced nebulizer. The I-neb AAD System and the AeroEclipse II nebulizer only deliver aerosol during inhalation, but the LC Sprint nebulizer also delivers during exhalation, albeit at a reduced rate. The breath-activated nebulizers claim greater reproducibility of DD. Each nebulizer was filled with 2.5 mL salbutamol sulphate (Salamol Steri-Neb, 2 mg/mL, IVAX Pharmaceuticals) and attached to an ASL 5000 breathing simulator (IngMar Medical Ltd) set to an adult breathing pattern (tidal volume = 500 mL, 10 breaths per minute, inhalation:exhalation ratio = 1:2). The AeroEclipse II nebulizer and the LC Sprint nebulizer were driven by 6 L/min medical air and run until sputter plus 60 seconds. The I-neb AAD System was fitted with a 0.5 mL dosing chamber and run until the end of aerosol generation. Delivery period was recorded for all nebulizers. The results indicated that the breath-activated nebulizers allow for a more reproducible DD. The DD results from the 2 breath-activated nebulizers were significantly different, and a considerably greater DD was delivered from the AeroEclipse II nebulizer, compared to the LC Sprint nebulizer or the I-neb AAD System. If such differences in DD were replicated in vivo, they could be translated into clinically relevant differences in drug dose available to the patient.

Introduction

We have previously reported on variability in dose between different types of nebulizer (venturi jet, breath-enhanced, and mesh nebulizers). 1,2 In this study we have extended the investigation to cover breath-activated nebulizers, and we report on a comparison of the delivered dose from a non-metered breath-activated nebulizer, a metered breath-activated nebulizer, and a breath-enhanced nebulizer.

Methods

Table 1. Nebulizers tested.

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Type</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td>LC Sprint</td>
<td>Breath-enhanced jet</td>
<td>PARI GmbH, Starnberg, Germany</td>
</tr>
<tr>
<td>AeroEclipse II</td>
<td>Breath-activated jet</td>
<td>Monaghan Medical Corp., Plattsburgh, USA</td>
</tr>
</tbody>
</table>
Nebulizer | Type | Manufacturer
--- | --- | ---
I-neb Adaptive Aerosol Delivery (AAD) System (with 0.5 mL metering chamber) | Adaptive aerosol delivery; breath-activated and breath-monitoring mesh | Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK

All equipment and materials were stabilized to ambient conditions for at least 30 minutes before use. Prior to testing, the nebulizers under test were washed according to the patient instructions supplied with the units. Three nebulizers of each brand (Table 1) were weighed, filled with 2.5 mL of 2 mg/mL salbutamol sulphate (albuterol sulfate; Salamol Steri-Neb, IVAX Pharmaceuticals, West Yorkshire, UK), reweighed, and connected via a filter (Filtrete; 3M, Bracknell, UK) to an ASL 5000 breathing simulator (IngMar Medical Ltd., Pittsburgh, PA, USA) set to generate an adult simulated breathing pattern (tidal volume = 500 mL, breaths per minute = 10, inhalation:exhalation ratio = 1:2). The connection between the filter and nebulizer mouthpiece was sealed with Parafilm M (Bemis Flexible Packaging, Neenah, WI, USA). The jet nebulizers were driven by 6 L/min wall air and run until 60 seconds after the onset of sputter (detected audibly by the operator); the mesh nebulizer was run until the end of aerosol generation. Each nebulizer was reweighed at the end of nebulization, to determine the residual volume, and dose collected on the filter was eluted for quantification by high performance liquid chromatography. Three nebulizers of each brand were tested in triplicate, and, in between tests, they were washed in warm, soapy water, rinsed, and dried in a drying cabinet. The mean delivered doses from the 3 nebulizer types were compared using t-tests.

Results

![Figure 1. Delivered dose from the AeroEclipse II nebulizer, the I-neb AAD System and the LC Sprint nebulizer (n = 9). Error bars denote 1 standard deviation from the mean.](image-url)
The shortest delivery period of 273 seconds was recorded for the LC Sprint. The I-neb AAD System had a delivery period of 452 seconds, and the longest delivery period was 831 seconds from the AeroEclipse II.

The results of the statistical analysis indicate that there was no significant difference between the dose delivered from the LC Sprint nebulizer or the I-neb AAD System. However, the dose delivered from the AeroEclipse II nebulizer was higher than that from either the I-neb AAD System or the LC Sprint nebulizer, a difference that was statistically significant. The relative standard deviation results for the 3 nebulizer types were: LC Sprint nebulizer = 31%, I-neb AAD System = 14%, and AeroEclipse II nebulizer = 9%.

Discussion

In recent years, the focus of developments in nebulizer technology has been geared towards making devices more patient/carer-friendly (e.g., faster, quieter, less environmental contamination with drug). In terms of providing minimal environmental contamination, the breath-activated nebulizers, which only deliver during inhalation, are significantly ahead of the other nebulizer types; delivering only during inhalation means that no drug is produced during exhalation and expelled to the atmosphere. However, the breath-activation can, as shown in this study, result in a much higher delivered dose from a standard nebule, unless the design of the device is such that the dose delivered to the patient is matched to the earlier devices that were used in the initial clinical studies through dose metering. The I-neb AAD System with 0.5 mL dosing chamber has an equivalent in vitro mean delivered dose to the LC Sprint nebulizer, which indicates that mean in vivo performance would be similar; however, the greater precision of the I-neb AAD System would give less variability in individual doses between treatments. The AeroEclipse II nebulizer produced a significantly higher dose, which is consistent with results from other studies; Coppolo et al found that the AeroEclipse II nebulizer delivered a dose of 791 µg of salbutamol sulphate, compared to the doses of 133-267 µg delivered from 4 conventional nebulizers. Similar differences were found in other studies. The higher dose from the AeroEclipse II nebulizer, compared to the LC Sprint nebulizer and the I-neb AAD System, could indicate that in vivo performance would be different. For drugs with wide therapeutic ranges, this may not be a great concern, but where a drug is used that has a narrower therapeutic range, it could be a cause for concern. The lower relative standard deviations seen with the breath-activated nebulizers indicate that both the inter-device and the intra-device doses delivered were more consistent than those delivered with the breath-enhanced nebulizer.

Conclusions

- Breath-activated nebulizers provided a more precise dose than a breath-enhanced nebulizer.
- The non-metered breath-activated nebulizer (AeroEclipse II) delivered a significantly higher dose than the metered breath-activated nebulizer (I-neb AAD System) and the breath-enhanced nebulizer (LC Sprint).

References