New ipratropium formulation to decrease nebulization time

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Received 6 March 2006; accepted 18 May 2006

\textbf{KEYWORDS} 
Aerosol; Jet nebulizer; Anticholinergic; Ipratropium bromide; Terbutaline; Nebulization time

\textbf{Summary} A new anticholinergic aerosol containing 0.5 mg ipratropium bromide dissolved in 1 mL of solution has been produced with the purpose of decreasing nebulization time for patients compared to the traditional formulation which is twice as voluminal (0.5 mg/2 mL, Boehringer-Ingelheim, France). The aim of this study was to compare aerosol characteristics (inhaled mass, particle size distribution and nebulization time) of these two formulations of ipratropium bromide, nebulized alone and with terbutaline (5 mg/2 mL, Astra Zeneca, Sweden), to determine whether the new formulation was equivalent to the old one. Four different jet nebulizers were used: Pari\textsuperscript{LC}, Atomisor NL9M\textsuperscript{R}, Sidestream\textsuperscript{R} and Mistyneb\textsuperscript{R}. Statistical analysis of the results showed that for all types of nebulizer, the inhaled mass of ipratropium bromide 0.5 mg/1 mL was significantly lower than the inhaled mass of ipratropium bromide 0.5 mg/2 mL, and that there was no statistical difference between the inhaled mass of ipratropium bromide 0.5 mg/1 mL+terbutaline 5 mg/2 mL and the inhaled mass of ipratropium bromide 0.5 mg/2 mL+terbutaline 5 mg/2 mL. The study also showed that the new formulation of ipratropium bromide (0.5 mg/1 mL) mixed with terbutaline allowed a 26% decrease in nebulization time compared to the old formulation (0.5 mg/2 mL) mixed with
terbutaline without changing aerosol characteristics (inhaled mass and particle size distribution). This leads to the conclusion that a 2 mL minimum volume is required for nebulization, and that nebulization of ipratropium bromide 0.5 mg/1 mL alone must be avoided.

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Introduction

An aerosolized medication is designed to be delivered in ventilated gas through the airways. This mode of administration is particularly suitable for treating respiratory disorders, as it allows the drug to enter the respiratory tract directly. As a consequence, doses required to obtain therapeutic effects are lower than for oral administration.1

Aerosols can be produced by different techniques, classified into three main categories: nebulizers (jet, ultrasonic, and vibrating mesh), metered dose inhalers and dry powder inhalers. Compared to metered dose inhalers and dry powder inhalers, nebulizers deliver high-drug doses with an aerosol deposition targeted at the desired site of action (i.e. pulmonary region).2 However, nebulizers require preparation prior to treatment and treatment time is longer.

Decreasing nebulization time would be of considerable value for aerosol therapy, as it might contribute to improved long-term compliance.

This study, based on the hypothesis that decreasing the volume to be nebulized would decrease the nebulization time, was designed to investigate to what extent decreasing drug volume may affect treatment efficiency.

A new formulation of ipratropium bromide (Atrovent® 0.5 mg/1 mL, Boehringer-Ingelheim, France) containing 0.5 mg of ipratropium bromide in 1 mL of solution was compared to the traditional formulation (Atrovent® 0.5 mg/2 mL, Boehringer-Ingelheim, France) containing 0.5 mg of ipratropium bromide in 2 mL of solution. This new formulation is therefore twice as concentrated with half the volume.

The aerosols produced with the two different ipratropium bromide formulations, nebulized alone and with terbutaline (Bricanyl® 5 mg/2 mL, AstraZeneca, Sweden) were characterized using four different jet nebulizers (PariLC®+, Atomisor NL9M®, Sidestream®, Mistyneb®). This study was focused on jet nebulizers only, as vibrating mesh nebulizers are not suitable for hospital use, and ultrasonic nebulizers have a residual volume which is too large for nebulization of volumes as small as 1 mL.

Materials and methods

Jet nebulizers

Four kinds of jet nebulizer were tested: Sidestream® nebulizer with Portaneb® compressor (Medic-Aid, UK), PariLC®+ nebulizer with Turbo Boy N® compressor (Pari, Germany), Atomisor NL9M® nebulizer with Atomisor Abox® compressor (Atomisor, DTF, France) and Mistyneb® nebulizer (Allegiance, France) with an air flow of 8 L/min (compressed air).

Since a given model of nebulizer can have significant performance variations from one unit to the other,5 three nebulizers of each model were tested, twice each, for each drug formulation.

Aerosol characteristics were measured in terms of inhaled mass (ipratropium bromide and terbutaline) and particle size distribution. The inhaled mass represents the quantity of drug actually delivered by a given nebulizer for a defined breathing pattern and period of time,3 i.e. the quantity of drug which is not lost in the nebulizer and can enter any region of the respiratory tract. This parameter characterizes the efficiency of the nebulization. The particle size distribution of the aerosol gives a precise idea of the deposition sites in the respiratory tract. It is characterized by the volume mean diameter (VMD), which is the diameter dividing the mass of aerosol into two equal halves, and the percentage of droplets with diameters between 1 and 5 μm, which corresponds to the respiratory fraction, i.e. the particles reaching the lungs.4 The nebulization time for each formulation was also recorded. Statistical analysis of the data was carried out to determine the effects of the new formulation on aerosol characteristics. The study should determine whether this new formulation, which was originally developed to be prescribed alone, is equivalent to the old one, in which case its aerosol characteristics would be good enough to be prescribed alone, or if it should be mixed with terbutaline for an acceptable efficiency.
Drug formulations

Four different drug formulations were tested: ipratropium bromide (0.5 mg/1 mL) alone, ipratropium bromide (0.5 mg/2 mL) alone, ipratropium bromide (0.5 mg/1 mL) mixed with terbutaline (5 mg/2 mL) and ipratropium bromide (0.5 mg/2 mL) mixed with terbutaline (5 mg/2 mL). Thus, 96 experiments were performed to test inhaled mass, with 96 additional experiments to test particle size distribution (four kinds of nebulizer, with three nebulizers of each kind tested twice each for the four drug formulations, totaling 96 experiments).

The osmolarities of ipratropium bromide (0.5 mg/2 mL) and ipratropium bromide (0.5 mg/1 mL) have been measured with an automatic osmometer (Hermann Roebling, Germany), and equaled respectively 317 and 329 milliosmol. Thus the new formulation maintained a similar osmolarity.

Inhaled mass

The inhaled mass of ipratropium bromide and terbutaline were measured, simulating patient breathing using a respiratory pump and collecting the aerosol on a filter. The nebulizer was connected to its associated compressor. An absolute filter (A/E, Gelman, Ann Arbor, MI) was positioned between the nebulizer and the respiratory pump (Harvard Apparatus, Ealing, UK) which was regulated according to the European Standard EN 13544-16: 15 breaths/min, 500 mL, \( I/E = 1 \), as shown in Fig. 1. The drug was introduced into the nebulizer. The respiratory pump was turned on, followed by the compressor. The total nebulization time, defined by the end of sputtering, was recorded. At the end of nebulization, the filter was folded and put into a tube (T420, Simport, Canada). Forty milliliter of solvent (1/1 0.001M hydrochloric acid and pure methanol) were added and the filter was ground. The tube was first centrifuged at 4000 rpm for 10 min at 13 °C (Eppendorf Centrifuge 5810R), and the supernatant was centrifuged again at 14000 rpm for 5 min at 13 °C (Eppendorf Centrifuge 5810R). The amount of active drug contained in the supernatant was measured by high performance liquid chromatography (HPLC) for ipratropium bromide and ultraviolet (UV) spectrophotometry for terbutaline.

Ipratropium bromide measurement by HPLC

The HPLC system consisted of a model 600 E delivery pump, a model Wisp 717 automatic sample injection device, a 2487 dual wavelength ultraviolet UV spectrophotometer detector, and a 996 photodiode array detector coupled to the UV detector outlet (all Waters, Saint Quentin en Yvelines, France). Analytic runs were processed by the Millenium PC software system (Waters). The mobile phase was composed of 1000 mL buffer solution (pH 3.2) plus 290 mL acetonitrile. The buffer solution was prepared by dissolving 2.51 g heptanesulphonic acid sodium salt monohydrate in 1000 mL water with pH adjusted to 3.2 with 0.05 M orthophosphoric acid. The flow rate was 1.5 mL/min and the UV detector was set to 210 nm. The photodiode array detector was used to check for peak purity.

Calibration curves were constructed from known amounts of ipratropium bromide nebulized on filters to obtain a linear relationship between the amount of ipratropium bromide nebulized on the filters and the area of the peaks. This relationship was used to calculate the amount of ipratropium bromide contained in the supernatant obtained from the various experiments, following injection of 40 \( \mu \)L of the supernatants.

Terbutaline measurement by UV spectrophotometry

The UV spectrophotometer (Perkin Elmer, Lambda20, USA) was calibrated to obtain a linear relationship between absorbance at 243 nm and the amount of terbutaline: precise amounts of terbutaline (2, 1, 0.2, 0.1, 0.02 mg) were deposited on filters (A/E, Gelman, Ann Arbor, MI) which were folded, put inside tubes (T420, Simport, Canada), ground in 20 mL of solvent (1/1 pure methanol and 0.001M hydrochloric acid) and centrifuged as described above, then the supernatants were tested using the UV spectrophotometer at 243 nm,
blank being made from the solvent alone. Terbutaline mass contained in the supernatants obtained from the various experiments was determined from this linear relationship.

**Nebulization time**

The total nebulization time was measured with a chronometer from the beginning of nebulization (compressor turned on) until the end of spluttering.

**Particle size distribution**

Particle size distribution was measured with a laser diffraction method (Mastersizer-X, Malvern, UK), as shown in Fig. 2. The mouthpiece exit of the nebulizer was placed close enough (1 cm) to the lens to avoid vignetting (loss of light due to scattering at wide angles), and far enough (2 cm) from the laser beam to avoid the mouthpiece interfering with the expanded laser beam, and the aerosol was directed towards the laser beam without producing measurement artefact. The aerosol passed through the laser beam and was directed towards an extraction pump (40 L/min) placed 5 cm from the laser beam.

The drug formulation was introduced into the nebulizer. The extraction pump and the compressor were turned on. At the end of nebulization, data acquisition was stopped, and the compressor was turned off.

The dispersion code was "polydisperse" and optic presentation "2QAA". Data inversion calculations to determine Volume Mean Diameter (VMD) and respiratory fractions, here defined as the percentage of particles with diameters between 1 and 5 μm which is a reflection of how the aerosol may deposit in the bronchial tree, were carried out using Mastersizer-X software.

**Statistical analysis of the results**

Statistical methods adapted to small samples were applied to the results to highlight the potential significant differences between the different drug formulations and nebulizers tested:

- Exact Kruskal–Wallis tests of Monte Carlo were performed to test the differences between the four formulations for one nebulizer, and between the four nebulizers for one formulation.
- Exact permutation tests were performed to test the differences between the two formulations of ipratropium bromide alone and between the two formulations of ipratropium bromide mixed with terbutaline for each nebulizer.
- Wilcoxon signed exact rank tests were performed to test the differences between terbutaline and ipratropium bromide inhaled mass for the two formulations of ipratropium bromide mixed with terbutaline for all the nebulizers taken together.

These statistical tests were performed using the StatXact software (version 3.0.2, Cytel Software Corporation).

Results were expressed in medians and the ranges in quartiles on the figures. A P value inferior to 0.05 was considered as a significant difference.

**Results**

**Inhaled mass**

Ipratropium bromide

Ipratropium bromide inhaled mass results were expressed in terms of mass of ipratropium bromide and are presented in Fig. 3 for ipratropium bromide nebulized alone and mixed with terbutaline.

The results differed significantly between the four formulations whatever the nebulizer: \( P = 0.001 \) for Sidestream nebulizer, \( P = 0.001 \) for PariLC+ nebulizer, \( P = 0.028 \) for NL9M nebulizer and \( P = 0.001 \) for Mistyneb nebulizer. Comparison of the samples (Fig. 3) indicated that ipratropium bromide 0.5 mg/1 mL was responsible for this statistical difference.

This was confirmed by the exact Kruskal–Wallis tests of Monte Carlo performed to test the differences between ipratropium bromide 0.5 mg/2 mL, ipratropium bromide 0.5 mg/1 mL+terbutaline...
5 mg/2 mL and ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL, which showed that there were no statistical differences between these three formulations: 

\[ P = 0.482 \text{ for Sidestream}^{\text{R}} \text{ nebulizer,} \]
\[ P = 0.993 \text{ for PariLC}^{\text{R}} \text{ nebulizer,} \]
\[ P = 0.740 \text{ for NL9M}^{\text{R}} \text{ nebulizer and} \]
\[ P = 0.869 \text{ for Mistyneb}^{\text{R}} \text{ nebulizer.} \]

Finally, there was a statistical difference between the two formulations of ipratropium bromide alone (\( P = 0.004 \) for Sidestream\(^{\text{R}}\) nebulizer, \( P = 0.002 \) for PariLC\(^{\text{R}}\) nebulizer, \( P = 0.041 \) for NL9M\(^{\text{R}}\) nebulizer and \( P = 0.002 \) for Mistyneb\(^{\text{R}}\) nebulizer), and there was no statistical difference between the two formulations of ipratropium bromide mixed with terbutaline (\( P = 0.582 \) for Sidestream\(^{\text{R}}\) nebulizer, \( P = 0.857 \) for PariLC\(^{\text{R}}\) nebulizer, \( P = 0.389 \) for NL9M\(^{\text{R}}\) nebulizer and \( P = 0.910 \) for Mistyneb\(^{\text{R}}\) nebulizer), indicating that ipratropium bromide 0.5 mg/1 mL should be mixed with terbutaline for nebulization.

The results of the four nebulizers were statistically different for the two formulations of ipratropium bromide alone (\( P = 0.0002 \) for ipratropium bromide 0.5 mg/1 mL and \( P = 0.0162 \) for ipratropium bromide 0.5 mg/2 mL) but not when used with the two formulations of ipratropium bromide mixed with terbutaline (\( P = 0.2535 \) for ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL and \( P = 0.0720 \) for ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL).

**Terbutaline**

Terbutaline inhaled mass was also measured. The results showed that terbutaline and ipratropium bromide behaved similarly i.e. the mass fraction of terbutaline inhaled mass was the same as the mass fraction of ipratropium bromide inhaled mass when these two drugs were mixed together: Wilcoxon signed exact rank tests gave \( P = 0.65 \) between terbutaline and ipratropium bromide inhaled mass for ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL, and \( P = 0.75 \) between terbutaline and ipratropium bromide inhaled mass for ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL for all the nebulizers taken together. This result was confirmed by Exact Pearson Tests which gave a correlation of 89% (\( P = 0.004 \)) for ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL, and 72% (\( P = 0.01 \)) for ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL.

**Nebulization time**

Nebulization times for ipratropium bromide alone and mixed with terbutaline are shown in Fig. 4.
As expected, the fill volume influenced significantly nebulization time for all the formulations of ipratropium bromide alone and mixed with terbutaline ($P < 0.0001$ for all the nebulizers).

The results of the four nebulizers were not statistically different in terms of nebulization time whatever the drug formulation: $P = 0.0757$ for ipratropium bromide 0.5 mg/1 mL, $P = 0.6872$ for ipratropium bromide 0.5 mg/2 mL, $P = 0.3554$ for ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL and $P = 0.0867$ for ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL.

The nebulization time had a strong linear regression with nebulization volume for all the nebulizers, as shown by the following linear regression equations ($x =$ nebulization volume (mL), $y =$ nebulization time (min)): $y = 2.42x - 0.29$ ($R^2 = 0.93$, $n = 24$) for Sidestream \textsuperscript{R} nebulizer, $y = 2.43x - 0.99$ ($R^2 = 0.89$, $n = 24$) for PariLC+ \textsuperscript{R} nebulizer, $y = 2.56x - 0.59$ ($R^2 = 0.83$, $n = 24$) for NL9M \textsuperscript{R} nebulizer and $y = 2.34x - 0.53$ ($R^2 = 0.94$, $n = 24$) for Mistyneb \textsuperscript{R} nebulizer. Fig. 5 shows an example of this linear regression on the graph of Mistyneb \textsuperscript{R} nebulizer.

**Particle size distribution**

Particle size distribution results were expressed in terms of VMD (Fig. 6) and respiratory fractions (Fig. 7). In terms of VMD, there were no significant differences between ipratropium bromide 0.5 mg/1 mL and ipratropium bromide 0.5 mg/2 mL for any nebulizer: $P = 0.552$ for Sidestream \textsuperscript{R} nebulizer, $P = 1.000$ for PariLC+ \textsuperscript{R} nebulizer, $P = 0.416$ for NL9M \textsuperscript{R} nebulizer and $P = 0.507$ for Mistyneb \textsuperscript{R} nebulizer. Neither were there significant differences between ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL and ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL and ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL.
### Figure 6
Volume mean diameter for ipratropium bromide alone and mixed with terbutaline ($n = 6$). Results expressed in medians and ranges in quartiles. "NS" represents no significant difference between the samples.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Volume Mean Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sidestream</td>
<td>4.6</td>
</tr>
<tr>
<td>PariLC+</td>
<td>3.6</td>
</tr>
<tr>
<td>NL9M</td>
<td>3.6</td>
</tr>
<tr>
<td>Misty neb</td>
<td>4.7</td>
</tr>
</tbody>
</table>

### Figure 7
Respiratory fraction (percentage of droplets between 1 and 5 µm) for ipratropium bromide alone and mixed with terbutaline ($n = 6$). Results expressed in medians and ranges in quartiles. "NS" represents no significant difference between the samples.

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Percentage of Droplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sidestream</td>
<td>67 ± 6</td>
</tr>
<tr>
<td>PariLC+</td>
<td>56 ± 5</td>
</tr>
<tr>
<td>NL9M</td>
<td>45 ± 4</td>
</tr>
<tr>
<td>Misty neb</td>
<td>47 ± 4</td>
</tr>
</tbody>
</table>
bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL: $P = 1.000$ for Sidestream\textsuperscript{R} nebulizer, $P = 0.827$ for PariLC+\textsuperscript{R} nebulizer, $P = 0.152$ for NL9M\textsuperscript{R} nebulizer and $P = 0.485$ for Mistyneb\textsuperscript{R} nebulizer.

Therefore, the admixture of terbutaline with ipratropium bromide did not change aerosol droplets size compared to ipratropium bromide nebulized alone.

The results were not significantly different in terms of respiratory fractions between the four formulations for any of the nebulizers: $P = 0.858$ for Sidestream\textsuperscript{R} nebulizer, $P = 0.476$ for PariLC+\textsuperscript{R} nebulizer, $P = 0.125$ for NL9M\textsuperscript{R} nebulizer and $P = 0.178$ for Mistyneb\textsuperscript{R} nebulizer.

However, the results were significantly different between the four nebulizers both in terms of VMD and respiratory fractions for all the formulations of ipratropium bromide alone and those mixed with terbutaline: $P < 0.0001$.

**Discussion**

The objective of this study was to compare the new ipratropium bromide formulation (0.5 mg/1 mL), which reduces the volume to be nebulized, with the traditional formulation (ipratropium bromide 0.5 mg/2 mL) when it is nebulized alone or mixed with terbutaline, in terms of inhaled mass, nebulization time and particle size distribution.

Ipratropium bromide alone and the admixture of terbutaline with ipratropium bromide had the same mass fraction of terbutaline and ipratropium bromide inhaled mass, and the same aerosol characteristics (particle size distribution). This may be due to the fact that both solutions have similar viscosities: 0.9923 \text{×} 10^{-3} \text{Poiseuilles (1.439 \text{×} 10^{-10} \text{lbf s/in}^{2}) for ipratropium bromide and 1.0087 \text{×} 10^{-3} \text{Poiseuilles (1.463 \text{×} 10^{-10} \text{lbf s/in}^{2}) for terbutaline.}\text{\textsuperscript{11}}

The inhaled mass of this new ipratropium bromide formulation (0.5 mg/1 mL) is significantly lower than the inhaled mass of ipratropium bromide 0.5 mg/2 mL, ipratropium bromide 0.5 mg/1 mL + terbutaline 5 mg/2 mL and ipratropium bromide 0.5 mg/2 mL + terbutaline 5 mg/2 mL. Thus, nebulization of ipratropium bromide 0.5 mg/1 mL alone cannot be recommended. In clinical practice, ipratropium bromide (anticholinergic) and terbutaline ($\beta$-agonist) are often administered simultaneously, as mixing these two bronchodilator classes may result in improving their efficiency, particularly in chronic obstructive pulmonary disease (COPD)\textsuperscript{12} or in asthma.\textsuperscript{13} Anticholinergic agents act as bronchodilators by blocking vagal bronchomotor activity. They have a relatively slow effect at onset, starting at around 10 min, with the peak effect occurring about 30–90 min after inhalation. $\beta$-Agonists are short-acting agents that produce bronchodilation within 3–5 min, reaching a peak at 15–30 min.\textsuperscript{12} Combination therapy of ipratropium and terbutaline with conventional doses has been shown to produce a significantly greater effect on forced expiratory volume in 1 s (FEV\textsubscript{1}) than ipratropium alone in obstructive lung diseases.\textsuperscript{14} This combination also leads to significant changes in functional residual capacity (FRC) in asthmatic children.\textsuperscript{13}

The new formulation of ipratropium bromide (0.5 mg/1 mL) mixed with terbutaline allowed a 26% decrease of nebulization time compared to the old formulation (0.5 mg/2 mL) mixed with terbutaline without changing aerosol characteristics (inhaled mass and particle size distribution). The new ipratropium bromide formulation (0.5 mg/1 mL), mixed with terbutaline, therefore allows nebulization time to be decreased while keeping the same inhaled mass, compared to the old 0.5 mg/2 mL formulation mixed with terbutaline, and potentially leads to improved clinical efficiency. Its major advantage of reducing nebulization time is also its major concern in clinical practice, since 1 mL is not recommended.

Statistical analysis of the results between the different nebulizers tested showed that particle size distributions (VMD and respiratory fractions) were significantly different between the four nebulizers for a single formulation, whereas they were similar with all the ipratropium bromide formulations for a single nebulizer. This indicates that the device used can strongly affect aerosol characteristics and therefore drug efficiency, whereas the ipratropium bromide formulation administered has no effect on the aerosol characteristics.

Factors influencing the total dose delivered to a patient’s airways include the initial volume fill, the efficiency with which the nebulized aerosol is made available for patient inhalation, and the amount of residual volume left in the nebulizer on cessation of the operation. This residual volume is typically ~1 mL, but may be as low as 0.5 mL or as high as 1.5 mL. The amount left is therefore not negligible compared to a typical volume fill (e.g. 2.5 mL). Thus, treatment time becomes critically dependent not only on the rate of aerosol inhaled mass and volume fill, but also on the minimum volume a nebulizer system requires to operate.\textsuperscript{15}

This study shows that initial volumes of 2, 3 and 4 mL containing the same amount of drug produced similar inhaled mass with the four nebulizers tested, whereas a fill volume of 1 mL resulted in
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References


decreased inhaled mass. This indicates that the nebulizers tested require a minimum volume of 2 mL but that increasing the volume to above 2 mL does not result in a better inhaled mass.

Other nebulizers with higher residual volumes than those tested in this study require more than 2 mL of drug to achieve an inhaled mass of about 25%. In particular, ultrasonic nebulizers are characterized by residual volumes ranging from 0.8 to 2 mL. These nebulizers have been demonstrated to be more efficient with increasing drug formulation volume.

On the other hand, new nebulizers which allow low residual volume, such as Aerogen’s OnQ™ Aerosol Generator, could be used to nebulize volumes smaller than 2 mL with the same efficiency in terms of inhaled mass as higher volumes, but they are not readily available in hospital settings in which disposable materials are preferred.

Decreasing the fill volume allows shorter nebulization time for the patient, but it is unclear whether the duration of nebulization has an impact on the respiratory tract deposition efficiency. The results obtained in terms of inhaled mass are similar for 2, 3 and 4 mL of ipratropium bromide formulations, but they may not reflect patient response exactly. A patient having an asthma attack may breathe better after a few minutes than at the very beginning of the nebulization, which would mean that a minimum nebulization duration is required. In this case, continuous nebulization therapy could be considered as a possible alternative until the patient is stable.

On the other hand, a more concentrated solution may produce a faster response from the patient. A high volume of nebulized drug could lead to a larger clearance and consequently more drug loss.

Thus, it could be of interest to carry out in vivo deposition imaging in patients’ respiratory Airways while inhaling 2, 3 and 4 mL of drug containing the same amount of active drug, to verify whether the results obtained in this study (i.e. equivalent inhaled mass for 2, 3 and 4 mL) would be similar for in vivo experiments.

Acknowledgements

This study was funded by Boehringer-Ingelheim, France.