Effect of continuous positive airway pressure combined to nebulization on lung deposition measured by urinary excretion of amikacin

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KEYWORDS
Nebulizer; Lung deposition; Continuous positive airway pressure; Urinary monitoring

Summary
Continuous positive airway pressure (CPAP) is frequently used in patients attending emergency units. Its combination with nebulization is sometimes necessary in those patients presenting with a CPAP dependency.

Study objective: To compare lung deposition of amikacin delivered by a classical jet nebulizer (SideStream; Medic-Aid; West Sussex, UK) used alone (SST) or coupled to a CPAP device (Boussignac; Vygon; Belgium).

Method: Amikacin (1 g) was nebulized with both devices in six healthy subjects during 5 min on spontaneous breathing. A 1-week wash-out period between each nebulization was applied. Lung deposition was indirectly assessed by urinary monitoring of excreted amount of amikacin.

Results: Total daily amount of amikacin excreted in the urine was significantly lower with CPAP than with SST (1.97% initial dose versus 4.88% initial dose, \( p < 0.001 \)) with a corresponding mean ratio CPAP/SST of 0.41. The residual amount of amikacin in the
nebulizer was higher with CPAP than with SST (607 mg versus 541 mg) but the difference was not significant ($p = 0.35$).

**Conclusion:** These data suggest that the amount of amikacin delivered to healthy lungs is 2.5-fold lower with CPAP than with SST for the same nebulization time and that the nebulization time when using CPAP should be increased to reach the same amount of drug delivered with a classical jet nebulizer.

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**Introduction**

The Boussignac valve delivery device was described in 1989. The device easily allows applying, at a low cost, continuous positive pressure that contributes to decrease the inspiratory work of breathing and to improve gas exchange. Its lightweight and small size may represent major advantages facilitating transport and mobilization of the apparatus that could be of particular interest for emergency units.

Nebulization is a frequently used method for drug delivery to the lungs of patients attending emergency units. A major aim is to administer drugs into the lungs as quick as possible and with lower systemic absorption than that obtained by other routes of administration. The amount of drug delivered to the lungs is essential to the clinical response. Various modalities of administration and devices have been developed and recent evidence-based guidelines assert nebulizers, pressurized metered-dose inhalers or powder inhalers can be equally efficient for delivering bronchodilators. Clinical setting must be taken into account in the choice of the device. In emergency units, nebulizers are often preferred to other inhaled modalities due to non-cooperation of patients. Respiratory distress and elder or pediatric patients account for poor cooperation.

In several clinical situations, the clinician may prefer to use continuous positive airway pressure (CPAP) simultaneously with nebulization but consequences of this association on lung deposition of nebulized drugs remain unclear. This study aimed at evaluating in a clinical setup the effects of the adjunction of a Boussignac valve positive airway pressure delivery to a nebulizer on the lung deposition of drug. Comparison was performed by sampling the daily urinary excretion of a single dose of nebulized amikacin which presents minimal oral absorption, negligible hepatic metabolism and short half-life. This procedure allows non-invasive estimation of the mass of drug deposited into the lungs and quantification of lung deposition because aminoglycosides are not absorbed from the digestive tract.

The subjects did not receive any antibiotic or aerosolized drug during the month preceding the experiments. All declared to be free from allergy to aminoglycosides.

**Nebulization**

A well-known and validated jet nebulizer (Sidestream; Medic-Aid; West Sussex, UK) (SST) was chosen as the reference nebulizer. It is driven by air supply and a flow of 10 L/min according to manufacturers’ recommendations.

In the Boussignac valve (CPAP Boussignac, Vygon, Belgium) (CPAP), the positive pressure is induced by injection of a gas under high flow through small deflected side channels. Gas propagation produces a hyperpressure creating a positive pressure to the patient side of the Boussignac valve and a depression to the other side (Fig. 1). CPAP was combined to the expiratory gate of Sidestream. Driving airflow of the valve was adapted according to pressure monitoring to obtain 6 cm H2O of positive airway pressure.

**Nebulized drug solution**

Amikacin sulfate (Bristol-Myers Squibb, Belgium) was dissolved in 4 mL 0.9% NaCl solution to a concentration of 250 mg/mL. The solution was nebulized during 5 min with each device. This duration was chosen following preliminary testing where sputtering point was considered as end-point of nebulization with Sidestream. Fill volume was less than maximal fill volume recommended (6 mL).

**Protocol**

Nebulizations were performed randomly with the SST alone or with the SST connected to the Boussignac valve.

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**Material and methods**

**Subjects**

After study approval by our Institutional medical Ethics Committee, six non-smoker healthy male volunteers (mean age $= 27.3 \pm 2.2$) were recruited. Each volunteer performed a spirometry according to the ATS/ERS guidelines and results were expressed in percentage of predicted value.

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**Figure 1** Illustration of the experimental combination of Boussignac valve with the nebulizer.
They were realized at the same time of the day, in the same room and at ambient temperature (mean = 23.2°C ± 0.8) during spontaneous continuous breathing. A wash out period of 1 week between both inhalations was respected for each subject. This period allows eliminating all residual drug due to its short half-life. Just before the experiments, the urinary bladder of the subjects was emptied. Then during the 24h following the nebulization, urine samples were collected at each spontaneous micturition. Their volume was precisely measured and the exact timing of the micturition was recorded.

Samples were assayed for amikacin by fluorescence polarization immuno-assay (FPIA) (TDx, Abbott Laboratories, Diagnostic Division, IL, USA).

Each subject inhaled the same solution with both devices in the same conditions. During the nebulization, the subjects were comfortably seated and breathed spontaneously through mouthpiece wearing a nose clip.

Measurements

During the nebulization, respiratory parameters such as tidal volume (Vt; L), respiratory frequency (RF; min⁻¹) and minute ventilation (VE; L min⁻¹) were monitored by inductance plethysmography (Respirtrace™, Ambulatory Monitoring Inc., Ardsley, NY, USA) after calibration with a spirometer.

An aliquot of 100 μL of initial and final solutions was sampled by pipetting in order to measure the amikacin concentration in the collector of the nebulizer. Residual volume was measured by pipetting after a 5 min rest period. Residual amount of drug was calculated by multiplying residual volume and final concentration.

Total daily amount of amikacin excreted in the urine (Cu max) was calculated from the sum of cumulative amikacin amount measured at each spontaneous micturition (Cu). The ratio between Cu max obtained after nebulization combined with positive airway pressure and Cu max obtained after nebulization alone allowed evaluating the efficiency of the nebulization while combined to a Boussignac valve. The constant of elimination (Ke) was calculated from the fitted curve of the cumulated amount of amikacin excreted in the urine plotted versus the time.

The equation is:

$$\text{Cu} = \text{Cu max} (1 - e^{-\text{Ke}t})$$

Statistical methods

Results are expressed as mean ± SD. Statistical tests were performed using SPSS 11.5 (Business unit of SAS, Cary, NC27513).

Residual amount was compared using an unpaired Student’s t-test. Student’s paired t-test was used for comparisons of pharmacokinetic parameters between the modalities.

Results

Mean anthropometric parameters of the six subjects were as follows: height = 179 ± 3 cm and weight = 77 ± 4 kg. They all presented a normal lung function (FVC = 97.8 ± 3.4% pred. and FEV1 = 93.6 ± 2.6% pred.).

The respiratory parameters are summarized in Table 1. Respiratory frequency was significantly lower when comparing CPAP with SST. No significant difference was found when comparing tidal volume and minute ventilation obtained with both devices.

Residual amount of amikacin (in the collector) was a slightly higher with CPAP than with SST (607 versus 541 mg) but the difference was not significant (p = 0.35).

Total daily amount of amikacin excreted in the urine was significantly lower with CPAP when comparing with SST (21.07 ± 2.95 versus 52.11 ± 4.18 mg) (p < 0.001). Proportion of the daily excreted amount and the initial dose of amikacin was, respectively, 4.9% and 1.9% for SST and CPAP (p < 0.001). The mean ratio Cu max (CPAP)/Cu max (SST) was 0.41 ± 0.05. The mean number of micturition was, respectively, 5.8 ± 1.2 and 5.8 ± 1.7 for CPAP and SST. The mean volume of urine was, respectively, 2.1L ± 0.6 and 2.2L ± 0.7 for CPAP and SST. Comparable values (0.171 versus 0.143, p = 0.27) were obtained for the elimination constant of the drug following nebulization with both devices.

Lung function, anthropometric parameters, and respiratory parameters were not correlated with Cu max.

Discussion

We here highlight that a lower dose of amikacin was delivered to healthy lungs with the combination of a Boussignac valve (CPAP) with a nebulizer (SST) than with the nebulizer (SST) alone.

Some of the methodological aspects of the study, compared to presently available published data should be addressed. According to a well-known feature,⁹ we found that a small fraction corresponding to 4.9% of initial dose was excreted in the urine when using the SST device.

CPAP produces a decrease of respiratory frequency¹⁰ and an increase of functional residual capacity. That should be beneficial to lung deposition.¹¹ Although we observed this decrease of respiratory frequency with CPAP, lung deposition was lower in this configuration. We can note that, excepted for I:E ratio, all respiratory parameters presented a higher coefficient of variation during CPAP than during nebulization alone. No correlation was found between pattern of breathing and lung deposition.

Table 1 Comparison of respiratory data obtained during nebulization with the continuous positive airway pressure (CPAP) device and the reference apparatus (SST) in six healthy subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPAP (L)</th>
<th>SST (L)</th>
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<tbody>
<tr>
<td>Vt</td>
<td>1.06 ± 0.4</td>
<td>0.76 ± 0.1</td>
</tr>
<tr>
<td>RF (min⁻¹)</td>
<td>9.1 ± 2.6*</td>
<td>13.7 ± 1.5</td>
</tr>
<tr>
<td>VE (L min⁻¹)</td>
<td>9.0 ± 1.9</td>
<td>10.3 ± 0.8</td>
</tr>
<tr>
<td>I:E</td>
<td>0.51 ± 0.05*</td>
<td>0.88 ± 0.07</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD. Vt, tidal volume; RF, respiratory frequency; VE, minute ventilation. *p < 0.001.
While the total daily urinary amount of aminoglycoside excreted was significantly lower with CPAP, constant of elimination that informs on the depth of the penetration of a nebulized drug into the lungs was not different. Similar kinetics suggests an identical localization of deposition without other precision on this localization. Then the difference in the urinary excretion should be due to different aerosol efficacy or intersubject variability. As the nebulizations were performed in paired conditions, the influence of anatomical and mechanical intersubject variability was eliminated as confounding factors.

In agreement with previous data, the concentration of the drug in the residual solution was increased at the end of nebulizations with both devices. Although not significant, higher amount of amikacin at the end of nebulizations with CPAP can be explained by a higher evaporation of the solvent due to flow induced into the collector.

Difference of lung dose without difference of residual amount could be explained by two elements. Due to lower I:E ratio during nebulization with CPAP, losses were probably higher during expiratory phase even though absence of filter on expiratory way do not allow to confirm this hypothesis. Indeed, Parkes had observed a decreased inhaled dose when a CPAP was combined with a nebulization. Moreover, additional flow produced by CPAP could increase impaction in mouth and then contribute to lower lung dose.

Moreover combining other modalities of positive airway pressure (BiPAP, IPV, IPPB) and nebulization have been studied with similar results.

Healthy subjects were enrolled to limit the effect of underlying lung diseases which can modify lung deposition, pattern of breathing and alveolocapillary permeability. Variability in urinary excretion of nebulized aminoglycosides and in rate of absorption have been previously reported in cystic fibrosis patients. All these elements justify the choice of healthy subjects to evaluate in a first time the drug and its clinical efficacy in patients requiring this combination CPAP-nebulization on lung administration of aminoglycoside aerosols in cystic fibrosis. Eur Respir J 2001;18(2):316–22.


