Intravenous versus Nebulized Ceftazidime in Ventilated Piglets with and without Experimental Bronchopneumonia

Comparative Effects of Helium and Nitrogen

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Background: Lung deposition of intravenous cephalosporins is low. The lung deposition of equivalent doses of ceftazidime administered either intravenously or by ultrasonic nebulization using either nitrogen–oxygen or helium–oxygen as the carrying gas of the aerosol was compared in ventilated piglets with and without experimental bronchopneumonia.

Methods: Five piglets with noninfected lungs and 5 piglets with Pseudomonas aeruginosa experimental bronchopneumonia received 33 mg/kg ceftazidime intravenously. Ten piglets with noninfected lungs and 10 others with experimental P. aeruginosa bronchopneumonia received 50 mg/kg ceftazidime by ultrasonic nebulization. In each group, the ventilator was operated in half of the animals with a 65%/35% helium–oxygen or nitrogen–oxygen mixture. Animals were killed, and multiple lung specimens were sampled for measuring ceftazidime lung tissue concentrations by high-performance liquid chromatography.

Results: As compared with intravenous administration, nebulization of ceftazidime significantly increased lung tissue concentrations (17 ± 13 vs. 383 ± 84 μg/g in noninfected piglets and 10 ± 3 vs. 129 ± 108 μg/g in piglets with experimental bronchopneumonia; P < 0.001). The use of a 65%/35% helium–oxygen mixture induced a 33% additional increase in lung tissue concentrations in noninfected piglets (141 ± 68 μg/g; P < 0.001) and no significant change in infected piglets (111 ± 104 μg/g).

Conclusion: Nebulization of ceftazidime induced a 5- to 30-fold increase in lung tissue concentrations as compared with intravenous administration. Using a helium–oxygen mixture as the carrying gas of the aerosol increased substantially additional increase in lung deposition in noninfected piglets but not in piglets with experimental bronchopneumonia.

BECAUSE of the limited lung penetration of intravenously administered antibiotics, there is increasing interest in the inhalation route. However, available data on antibiotic lung deposition after aerosol is scarce, and nebulization is not considered a credible alternative to the intravenous route for treating ventilator-associated pneumonia. During mechanical ventilation, a significant part of the particles emitted by a nebulizer impacts the ventilatory circuits and the tracheobronchial tree before reaching the distal lung. The use of an ultrasonic nebulizer and the optimization of ventilatory settings during the nebulization period tend to limit extrapulmonary deposition and enhance distal lung penetration.1,2 We have recently demonstrated, in mechanically ventilated piglets with Escherichia coli bronchopneumonia treated with amikacin, that substituting the intravenous route for the inhalation route allows a 10-fold increase in amikacin lung tissue concentrations.1,4 With such a concentration-dependent antibiotic, the high peak lung tissue concentrations resulting from nebulization were associated with rapid and impressive bacteria killing.2,4

As far as time-dependent antibiotics such as cephalosporins are concerned, tissue concentrations greater than minimal inhibitory concentrations should be permanently maintained at the site of infection, and intermittent high peak tissue concentrations may not be sufficient to provide a bactericidal effect. When minimal inhibitory concentrations increase, this goal cannot be achieved with the intravenous route. As experimentally observed with aminoglycosides, the nebulization of ceftazidime could be an attractive alternative to the intravenous route for treating ventilator-associated pneumonia caused by impaired sensitivity strains, and any means of improving lung deposition during nebulization may be of interest for obtaining and maintaining sufficiently high lung tissue concentrations.

A recent in vitro study has shown that the aerosol delivered to an artificial lung during mechanical ventilation could be markedly improved by using a helium–oxygen mixture as the operating gas for ventilation.5 However, the effects of the helium–oxygen mixture on the in vivo lung deposition of the aerosol was not directly investigated. The current study performed in mechanically ventilated piglets with noninfected lungs and experimental bronchopneumonia was conducted to compare lung deposition of equivalent doses of ceftazidime administered intravenously or by an ultrasonic nebulizer and to assess whether a helium–oxygen mixture could further increase lung tissue concentrations. In addition, extrapulmonary deposition and the size of particles were measured to compare the physical character-

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Hemodynamic parameters, airway pressures, respiratory gas tensions, and the fraction of inspired oxygen were measured every 2 h during 24 h with a fixed tidal volume of 15 ml/kg. 

Bronchial Inoculation and Mechanical Ventilation
Fifteen piglets were inoculated with a suspension of Pseudomonas aeruginosa (identification by an API 32E kit; bioMérieux, Marcy l’Etoile, France). The initial suspension was diluted to a concentration of 10^5 colony-forming units/ml. A volume of 40 ml was selectively inoculated in each lower main bronchus using fiberoptic bronchoscopy. The inoculated piglets were then ventilated during 24 h with a fixed tidal volume of 15 ml/kg. Hemodynamic parameters, airway pressures, respiratory compliance, and blood gases were determined every 6 h. Throughout the protocol, the fraction of inspired oxygen was increased to maintain arterial oxygen tension above 80 mmHg.

Aerosol Generation
As shown in figure 1, an ultrasonic nebulizer (Atomisor

Materials and Methods
Animal Preparation
Thirty healthy bred domestic Largewhite-Landrace piglets, aged 3 months and weighting 20 ± 1 kg, were anesthetized and orotracheally intubated in the supine position with a 7.5 Hi-Lo Jet Mallinckrodt tube (Mallinckrodt Inc., Argyle, NY). The piglets were then turned in their physiologic position (prone position), ventilated using a Cesar ventilator (Taema, Antony, France), and monitored in the experimental intensive care unit. The study, including care of the animals involved, was conducted according to the official edict presented by the French Ministry of Agriculture (Paris, France) and the recommendations of the Helsinki Declaration. Thus, these experiments were conducted in an authorized laboratory and under the supervision of an authorized researcher (C.-H. M.). Arterial blood gas, tracheal airway pressure, and pressure-volume curve were measured as previously described.

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Aerosol Generation
As shown in figure 1, an ultrasonic nebulizer (Atomisor
Positive end-expiratory pressure had no influence on the oxygen group and 68% in the nitrogen–oxygen group.

The metric mean diameter was 3.59 μm in the helium–oxygen group, whereas the respirable range of particles, defined as the percentage of particles with aerodynamic size less than 0.5 μm in the helium–oxygen group versus 50 ± 4% (500 ± 40 μg) in the nitrogen–oxygen group (not significant), a dose closely equivalent to the intravenous dose (660 ± 30 mg). In the helium–oxygen group, 11% of the dose was retained in the chamber of the nebulizer, 7% was retained in the inspiratory circuits, 6% was retained in the endotracheal tube, and 14% was retained in the expiratory filter. In the nitrogen–oxygen group, 15% of the dose was retained in the chamber of the nebulizer, 10% was retained in the inspiratory circuits, 10% was retained in the endotracheal tube, and 15% was retained in the expiratory filter.

As shown in table 1, animals with experimental bronchopneumonia experienced a significant deterioration of gas exchange and respiratory mechanics as compared with noninfected piglets. The nature of the operating gas had no influence on arterial blood gas or respiratory mechanics. The aerosols, performed in 20 ± 7 min in all groups, were clinically well tolerated. No bronchospasm or blood gas alteration was observed.

As shown in figure 2, in noninfected animals, ceftazidime lung tissue concentrations were 17 ± 13 μg/g after intravenous administration, 383 ± 84 μg/g after nitrogen–oxygen nebulization, and 576 ± 141 μg/g after helium–oxygen nebulization (P < 0.001). The 33% increase in mean ceftazidime lung tissue concentrations observed when the ventilator was operated with the 65%/35% helium–oxygen mixture was highly significant (P < 0.001). No significant relation was found between extrapulmonary deposition and ceftazidime lung tissue concentrations (P = 0.063).

In piglets with experimental bronchopneumonia (fig. 3), ceftazidime lung tissue concentrations were 10 ± 3 μg/g after intravenous administration versus 129 ± 108 μg/g after nitrogen–oxygen nebulization (P < 0.001). The mean ceftazidime lung tissue concentrations were not significantly different according to the gas mixture.

Table 1. Effects of 65%/35% He–O2 and 65%/35% N2–O2 Mixture on Blood Gas and Respiratory Mechanics in Piglets with Noninfected Lungs and Experimental Bronchopneumonia

<table>
<thead>
<tr>
<th>Aerosol Type</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td></td>
<td>Pao2, mmHg</td>
<td>PaCO2, mmHg</td>
<td>Pplat, cm H2O</td>
<td>Crs, ml/cm H2O</td>
<td>Pao2, mmHg</td>
<td>PaCO2, mmHg</td>
<td>Pplat, cm H2O</td>
<td>Crs, ml/cm H2O</td>
</tr>
<tr>
<td>Noninfected N2–O2 Group</td>
<td>167 ± 15</td>
<td>170 ± 21</td>
<td>44 ± 3</td>
<td>43 ± 3</td>
<td>24 ± 2</td>
<td>21 ± 2</td>
<td>34 ± 4</td>
<td>37 ± 4</td>
</tr>
<tr>
<td>Noninfected He–O2 Group</td>
<td>149 ± 20</td>
<td>176 ± 12</td>
<td>39 ± 2</td>
<td>39 ± 3</td>
<td>20 ± 4</td>
<td>21 ± 2</td>
<td>37 ± 3</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Bronchopneumonia N2–O2 Group</td>
<td>94 ± 33</td>
<td>92 ± 35</td>
<td>47 ± 9</td>
<td>49 ± 7</td>
<td>28 ± 8</td>
<td>29 ± 5</td>
<td>28 ± 4</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>Bronchopneumonia He–O2 Group</td>
<td>87 ± 28</td>
<td>90 ± 38</td>
<td>46 ± 5</td>
<td>42 ± 3</td>
<td>31 ± 6</td>
<td>29 ± 8</td>
<td>31 ± 6</td>
<td>30 ± 5</td>
</tr>
</tbody>
</table>

*Crs = static respiratory compliance defined as the slope of the pressure–volume curve; He–O2 = helium–oxygen; N2–O2 = nitrogen–oxygen; PaCO2 = arterial carbon dioxide tension; PaO2 = arterial oxygen tension; Pplat = inspiratory plateau airway pressure.*
tissue samples. Tissue concentrations are expressed in middle, and lower lobes to obtain representative distal lung five juxtapleural specimens were collected from the upper, middle, and lower lobes to obtain representative distal lung tissue samples. Tissue concentrations are expressed in µg/g. Nebulization dramatically increased ceftazidime lung deposition, and there was an additional 33% increase in lung tissue concentrations when using the helium–oxygen mixture (\( P < 0.001 \)). \( \text{He} = \) helium; \( \text{O}_2 = \) oxygen.

Fig. 2. Lung tissue concentrations of ceftazidime obtained in 15 piglets with noninfected lungs. Fifteen minutes after intravenous administration of 33 mg/kg ceftazidime (\( n = 5 \)) or administration of 1 g ceftazidime by an ultrasonic nebulizer, using 65%/35% nitrogen–oxygen (\( n = 5 \)) or helium–oxygen (\( n = 5 \)) as the operating gas of the ventilator, animals were killed, and five juxtapleural specimens were collected from the upper, middle, and lower lobes to obtain representative distal lung tissue samples. Tissue concentrations are expressed in µg/g. Nebulization dramatically increased ceftazidime lung deposition, and there was an additional 33% increase in lung tissue concentrations when using the helium–oxygen mixture (\( P < 0.001 \)). \( \text{He} = \) helium; \( \text{O}_2 = \) oxygen.

Fig. 3. Lung tissue concentrations of ceftazidime obtained in 15 piglets with experimental bronchopneumonia. Fifteen minutes after intravenous administration of 33 mg/kg ceftazidime (\( n = 5 \)) or administration of 1 g ceftazidime by an ultrasonic nebulizer, using 65%/35% nitrogen–oxygen (\( n = 5 \)) or helium–oxygen (\( n = 5 \)) as the operating gas of the ventilator, animals were killed, and five juxtapleural specimens were collected from the upper, middle, and lower lobes to obtain representative distal lung tissue samples. Tissue concentrations are expressed in µg/g. Nebulization dramatically increased ceftazidime lung deposition. No increase in lung tissue concentrations was observed when using the helium–oxygen mixture rather than the nitrogen–oxygen mixture. \( \text{He} = \) helium; \( \text{NS} = \) not significant; \( \text{O}_2 = \) oxygen.

\( (129 \pm 108 \) µg/g with nitrogen–oxygen vs. \( 111 \pm 104 \) µg/g with helium–oxygen) and remained lower than in noninfected animals (\( P = 0.01 \)).

Discussion

In anesthetized and mechanically ventilated piglets with noninfected lungs, nebulization of ceftazidime resulted in a dramatic increase in lung tissue concentrations as compared with the concentrations observed after intravenous administration of an equivalent dose. In addition, when the ventilator was operated with a 65%/35% helium–oxygen mixture, an additional 33% increase in ceftazidime lung tissue concentration was observed. Because specimens removed from subpleural lung regions were composed of alveolar structures and distal bronchioles, these results clearly demonstrate that the helium–oxygen mixture markedly increased ceftazidime lung deposition and not only proximal airway deposition. Unfortunately, this beneficial effect was not observed in animals with infected lungs, thereby limiting the clinical relevance of the former finding.

Lung deposition of aerosolized particles during mechanical ventilation depends on several factors: the size of the particles; the extrapulmonary deposition into respiratory circuits; the physical characteristics of the gas flow reaching the distal lung; and the time allotted for sedimentation of particles within the bronchioloalveolar compartment and the alveolar aeration, which depends on the permeability of distal bronchioles. In the presence of normal distal lung aeration, particles between 3 and 5 µm have the highest probability of lung deposition, whereas particles larger than 5 µm generally impact the respiratory circuits, the endotracheal tube, or the proximal bronchi. During mechanical ventilation, antibiotic inhalation can be achieved by jet or ultrasonic nebulization. In the first technique, the gas operating the ventilator also operates the jet nebulizer: It generates particles through the Bernoulli effect and entrains the aerosol toward the distal lung.\(^{14}\) With an ultrasonic nebulizer, size distribution of particles results from the physical characteristics of the quartz vibrations and is not influenced by the inspiratory gas, which plays no role in aerosol generation. In the current study, as expected, the helium–oxygen mixture did not modify the mean volumetric diameter of particles. More surprisingly, the use of helium did not significantly reduce the aerosol extrapulmonary deposition. Previous laboratory studies have shown that decreasing the physical density of the carrying gas by replacing nitrogen by helium has opposite effects on aerosol performance: It reduces the efficiency of jet nebulizers by reducing the pressure decrease across the jet orifice\(^{5,14}\) but increases aerosol delivery of metered-dose inhalers by reducing flow turbulence within ventilatory circuits.\(^{5}\) The impaction of
aerosolized particles on respiratory circuits and bronchial walls is markedly influenced by tidal volume, inspiratory flow rate, and humidification of inspired gas. Wall impaction is minimal with non humidified gas delivered at flow rates less than 40 l/min and increases with higher flows. In fact, wall impaction of particles markedly increases when the flow changes from laminar to turbulent. In the current study, the gas mixture was delivered at a low flow rate of 11 l/min required for providing a 300-ml (15-ml/kg) tidal volume to piglets. Very likely, turbulences of the nitrogen–oxygen flow within respiratory circuits and proximal bronchi were minimal with this flow rate, thereby limiting wall impaction. Using a helium–oxygen mixture did not further decrease gas flow turbulences and therefore did not further reduce extrapulmonary deposition as observed in previous in vitro experiments using higher flows. In fact, the helium–oxygen mixture reduces extrapulmonary deposition of aerosolized particles only when the flow profile within respiratory circuit is changed from turbulent to laminar. Inspiratory flow rates greater than 40 l/min are commonly delivered for ventilation of patients with acute lung injury. Such high flows, by producing turbulences in the ventilator circuits and proximal airways, promote wall impaction of aerosolized particles when a nitrogen–oxygen mixture is used. The administration of a helium–oxygen mixture converts turbulent flows into laminar flows and thereby limits wall impaction and decreases extrapulmonary deposition. In the current study, such an effect was not observed because of the low inspiratory flow used in piglets. As a consequence, the 33% increase in ceftazidime deposition in noninfected animals observed with the 65%/35% helium–oxygen mixture was likely explained by helium-induced decreases in turbulences within distal bronchioles. In the distal bronchial tree, the reduction of the bronchiolar diameter and the great number of bronchiolar divisions physiologically produces turbulences even for low flows and promotes wall impaction of particles. Helium, by reducing gas density, reduces turbulences and promotes distal lung deposition, provided that bronchioles remain permeable.

In the presence of ventilator-associated pneumonia, bronchiolitis results in bronchial plugs impairing downstream alveolar aeration. As a consequence, the 65%/35% helium–oxygen mixture did not provide additional lung deposition because the loss of alveolar aeration became predominant over flow turbulence. As far as clinical use is concerned, the efficiency of nebulized antibiotics is established to treat tracheobronchial colonization during cystic fibrosis or to prevent ventilator-associated pneumonia. Even if they have been used successfully in several cases of severe bronchopneumonia caused by multiresistant P. aeruginosa, nebulized antibiotics are not recognized as an efficient treatment of ventilator-associated pneumonia. However, the potential advantages of nebulization over intravenous administration deserve to be outlined. As demonstrated in the current study, nebulization results in a marked increase in lung tissue concentrations. For a time-dependent antibiotic such as ceftazidime, concentrations equal to the minimal inhibitory concentration must be maintained over time at the site of the infection to kill bacteria. When the minimal inhibitory concentration increases, the weak lung deposition of intravenous ceftazidime associated with alterations of pharmacokinetics present in critically ill patients does not allow sufficient lung concentrations in most patients. The microorganism is then considered to be resistive to the antibiotic. The current study demonstrates that high ceftazidime lung tissue concentrations can be achieved in healthy and bronchopneumonic animals after ultrasonic nebulization. During bronchopneumonia, the use of a helium–oxygen mixture does not provide additional lung tissue deposition. It must be pointed out that only peak ceftazidime tissue concentrations were measured in the current study. Trough tissue concentrations are more relevant regarding time-dependent antibiotics, and additional studies are required to assess whether sufficient trough tissue concentrations can be maintained during the interval between two nebulized doses of ceftazidime.

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References


