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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 (576 ± 141 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 induced a substantial 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 are 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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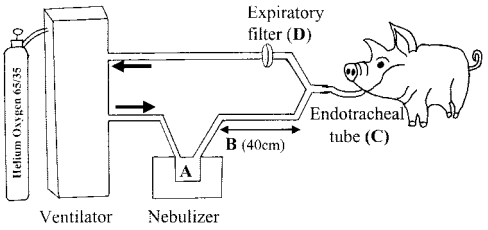

Fig. 1. Diagram showing the experimental setting. The ultrasonic nebulizer is positioned 40 cm before the Y piece connecting inspiratory and expiratory limbs to the proximal tip of the endotracheal tube. An expiratory filter is inserted on the expiratory limb, just after the Y piece. Extrapulmonary deposition is defined as the amount of ceftazidime trapped in *A*, *B*, *C*, and *D* after nebulization.

istics of the ceftazidime aerosol when the nebulizer was operated by the two different gas mixtures.

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.[1–4,6–8] This 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.[8,9]

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 10^6 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 MegaHertz; Diffusion Technique Française, Saint-Etienne, France) was placed in the inspiratory limb, 40 cm proximal to the Y piece.[10,11] A filter with a pore size of less than 0.3 μm (Hygrobac; Mallinckrodt Medical, Mirandola, Italy) was placed on the expiratory limb to collect expired aerosolized particles. As previously recommended,[11,12] experiments were performed without humidification of inspired gas, and aerosol delivery was optimized by using the following ventilatory settings: tidal volume of 15 ml/kg, constant inspiratory flow rate of 11 l/min, respiratory rate of 15 breaths/min, inspiratory:expiratory ratio of 1:1, and positive expiratory pressure of 5 cm H_2O.

Because tidal volume is measured by a hot wire on the Cesar ventilator, a new calibration was performed when the 65%/35% helium–oxygen mixture was used. Using a pneumotachograph (Hans Rudolph Inc., Kansas City, MO) calibrated with a supersyringe containing a 65%/35% helium–oxygen mixture, the relation between set and delivered tidal volume was measured.

After the animals were killed, all ventilatory circuits, including the endotracheal tube and the expiratory filter, were washed separately in a fixed volume of distilled water to measure extrapulmonary deposition.[1,2] In a separate *in vitro* bench study, the volumetric mean diameter and the proportion of particles between 1 and 5 μm were measured with a laser velocimeter (Malvern Instrument, Worcestershire, UK) at the distal end of the endotracheal tube[1,2] and expressed as the mean of three consecutive measurements performed with each operating gas.

Study Design

Ten healthy piglets received a single 1-g dose of ceftazidime powder diluted in 15 ml sterile water through ultrasonic nebulization. A 65%/35% helium–oxygen mixture (noninfected helium–oxygen group; n = 5) or a 65%/35% nitrogen–oxygen mixture (noninfected nitrogen–oxygen group; n = 5) was used for ventilation during the period of nebulization. Five other piglets received a standard dose of ceftazidime (33 mg/kg) by intravenous infusion (noninfected intravenous group).

Twenty-four hours after the bacterial inoculation, 10 piglets with experimental bronchopneumonia received a single 1-g dose of ceftazidime by ultrasonic nebulization during ventilation with a 65%/35% helium–oxygen mixture (infected helium–oxygen group; n = 5) or with a 65%/35% nitrogen–oxygen mixture (infected nitrogen–oxygen group; n = 5), and 5 other piglets received a standard dose of ceftazidime (33 mg/kg) by intravenous infusion (infected intravenous group). Arterial blood gas, airway pressure, and static compliance were measured just before nebulization.

As previously described,[1,2] the piglets were killed by exsanguination 15 min after completion of nebulization or intravenous infusion, and five lung samples per animal

Table 1. Effects of 65%/35% He–O_2 and 65%/35% N_2–O_2 Mixture on Blood Gas and Respiratory Mechanics in Piglets with Noninfected Lungs and Experimental Bronchopneumonia

	Noninfected N_2–O_2 Group		Noninfected He–O_2 Group		Bronchopneumonia N_2–O_2 Group		Bronchopneumonia He–O_2 Group	
	Before Aerosol	After Aerosol	Before Aerosol	After Aerosol	Before Aerosol	After Aerosol	Before Aerosol	After Aerosol
Pa_{O_2}, mmHg	167 ± 15	170 ± 21	149 ± 20	176 ± 12	94 ± 33	92 ± 35	87 ± 28	90 ± 38
Pa_{CO_2}, mmHg	44 ± 3	43 ± 3	39 ± 2	39 ± 3	47 ± 9	49 ± 7	46 ± 5	42 ± 3
P_{Plat}, cm H_2O	24 ± 2	21 ± 2	20 ± 4	21 ± 2	28 ± 8	29 ± 5	31 ± 6	29 ± 8
C_{rs}, ml/cm H_2O	34 ± 4	37 ± 4	37 ± 3	38 ± 3	28 ± 4	29 ± 2	31 ± 6	30 ± 5

C_{rs} = static respiratory compliance defined as the slope of the pressure–volume curve; He–O_2 = helium–oxygen; N_2–O_2 = nitrogen–oxygen; Pa_{CO_2} = arterial carbon dioxide tension; Pa_{O_2} = arterial oxygen tension; P_{plat} = inspiratory plateau airway pressure.

were collected from the upper, middle and lower lobes. Postmortem tissue samples were cryomixed in nitrogen, weighed, and homogenized, and ceftazidime concentrations were measured by high-performance liquid chromatography.[13]

Statistical Analysis

Data were analyzed using Statview Software (SPSS, Inc., San Raphael, CA). Tissue ceftazidime concentrations were compared among the three groups using the Kruskal-Wallis one-way analysis of variance on ranks test followed by the Dunn *post hoc* comparison test. The correlation between the delivered dose and the lung concentration of ceftazidime was determined by linear regression (after the Kolmogorov-Smirnov test had confirmed that distribution of data were normal). A P value less than 0.05 was considered as significant. All data are expressed as mean ± SD.

Results

When using the 65%/35% helium–oxygen mixture, delivered tidal volumes were always higher than set tidal volumes. The relation between delivered tidal volume and set tidal volume was linear, and a correction factor of 1.5 had to be applied to set tidal volume. To obtain a delivered tidal volume of 300 ml, the tidal volume had to be set at 200 ml on the ventilator.

The use of a helium–oxygen mixture did not modify the aerodynamic size distribution of particles: The volumetric mean diameter was 3.59 μm in the helium–oxygen group and 3.81 μm in the nitrogen–oxygen group, whereas the respirable range of particles, defined as the percentage of particles with aerodynamic size ranging between 1 and 5 μm, was 80% in the helium–oxygen group and 68% in the nitrogen–oxygen group. Positive end-expiratory pressure had no influence on the aerodynamic size distribution of particles. Similarly, the helium–oxygen mixture did not reduce the extrapulmonary deposition of the aerosol. Of the initial amount of ceftazidime placed in the nebulizer, 62 ± 7% (620 ± 70 mg) entered the tracheobronchial tree in the helium–oxygen group *versus* 50 ± 4% (500 ± 40 mg) 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

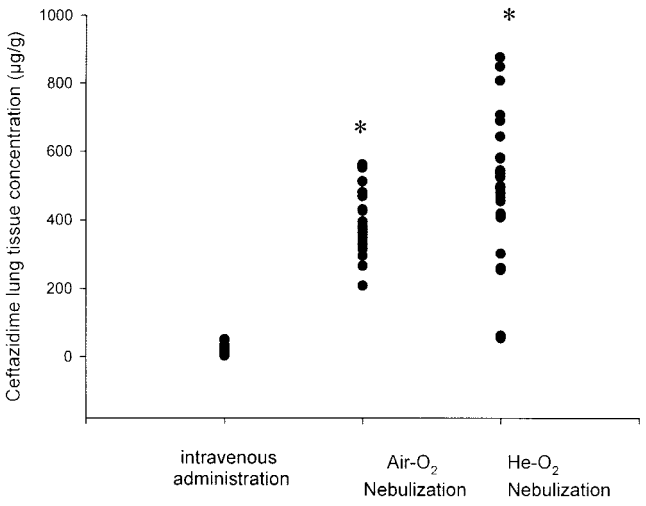

Fig. 2. Lung tissue concentrations of ceftazidime obtained in 15 piglets with noninfected lungs. Fifteen minutes after intravenous administration of 33 mg/kg ceftazidime (n = 5) or administration of 1 g ceftazidime by an ultrasonic nebulizer, using 65%/35% nitrogen–oxygen (n = 5) or helium–oxygen (n = 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 rather than the nitrogen–oxygen mixture (* $P < 0.001$). He = helium; O_2 = oxygen.

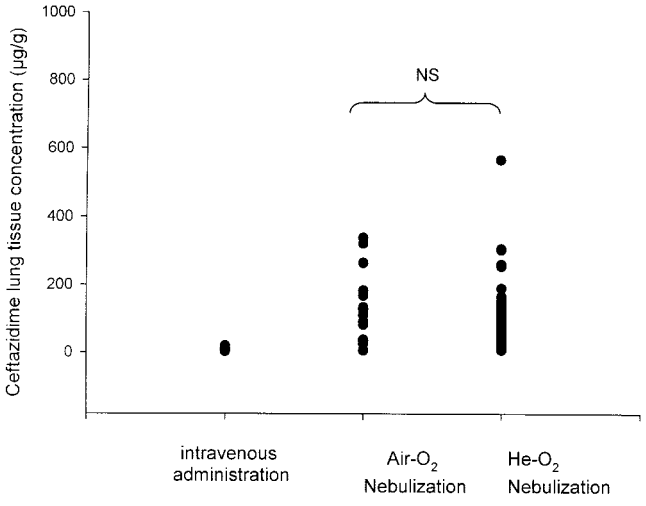

Fig. 3. Lung tissue concentrations of ceftazidime obtained in 15 piglets with experimental bronchopneumonia. Fifteen minutes after intravenous administration of 33 mg/kg ceftazidime (n = 5) or administration of 1 g ceftazidime by an ultrasonic nebulizer, using 65%/35% nitrogen–oxygen (n = 5) or helium–oxygen (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 rather than the nitrogen–oxygen mixture. He = helium; NS = not significant; O_2 = oxygen.

(129 ± 108 µg/g with nitrogen–oxygen *vs.* 111 ± 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 nonhumidified 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.[5] 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.[5] 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.[5]

In the presence of ventilator-associated pneumonia, bronchiolitis results in bronchial plugs impairing downstream alveolar aeration.[15] 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[16–20] or to prevent ventilator associated pneumonia.[21] Even if they have been used successfully in several cases of severe bronchopneumonia caused by multiresistant *P. aeruginosa*,[22,23] 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[24] 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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