Penetration of Gentamicin Into the Alveolar Lining Fluid of Critically Ill Patients With Ventilator-Associated Pneumonia*

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Study objectives: To estimate the penetration of gentamicin into lung tissue by measuring its concentrations in alveolar lining fluid (ALF) and blood in critically ill patients with ventilator-associated pneumonia (VAP).

Patients and interventions: The study population consisted of 24 patients who were admitted to an ICU for respiratory failure and developed VAP. Patients were scheduled to undergo bronchoscopy with BAL after IV administration of a once-daily, 240-mg schedule of gentamicin for the treatment of VAP. Patients were assigned at random to one of four groups of six patients each according to the scheduled time for bronchoscopy (1, 2, 4, or 6 h, respectively). A serum sample was obtained at 0.5 h (n = 24), and both serum and ALF samples (n = 6) were collected at each of the above specified times for measurement of antibiotic concentrations.

Measurements and results: Mean ± SEM gentamicin concentrations in the ALF were 2.95 ± 0.37, 4.24 ± 0.42, 3.10 ± 0.39, and 2.65 ± 0.35 μg/mL at 1, 2, 4, and 6 h, respectively, after the start of antibiotic infusion. Maximum gentamicin concentrations in serum (13.39 ± 0.91 μg/mL, n = 24) and ALF (4.24 ± 0.42 μg/mL, n = 6) were achieved at 0.5 h and 2 h, respectively, giving a penetration ratio of 0.32. The mean ratios of ALF/serum concentrations between 1 h and 6 h ranged from 0.30 to 1.14. After completion of the distribution phase, a significant positive correlation (p < 0.02) was found between gentamicin concentrations in the serum and ALF.

Conclusions: Once-daily IV administration of 240-mg gentamicin achieved average peak antibiotic concentrations of 4.24 μg/mL in the ALF 2 h after administration, and an ALF/serum penetration ratio of 32%. Higher gentamicin doses to produce higher peak blood levels than those found with the study dose are necessary to obtain active alveolar concentrations against less sensitive microorganisms in the treatment of VAP in ICU patients.

(CHEST 2005; 128:545–552)

Key words: alveolar lining fluid; BAL; gentamicin; penetration; ventilator-associated pneumonia

Abbreviations: ALF = alveolar lining fluid; APACHE = acute physiology and chronic health evaluation; Cmax = maximum gentamicin concentration; Fio2 = fraction of inspired oxygen; Gent = gentamicin concentration; MIC = minimum inhibitory concentration; MV = mechanical ventilation; PEEP = positive end-expiratory pressure; Valf = apparent volume of ALF; VAP = ventilator-associated pneumonia; Vbal = volume of BAL; VT = tidal volume

Pneumonia and bacteremia are the two most prevalent serious nosocomial infections in critically ill patients,1,2 and the risk of pneumonia is increased 3- to 10-fold in the intubated patient receiving mechanical ventilation (MV) exhibiting particularly high mortality rates (24 to 76%).3 Despite the use of aminoglycosides for > 30 years, these antimicrobial agents continue to play a significant role in the treatment of Gram-negative bacil-
lary infections. These pathogens are responsible to a large extent for the number of deaths associated with nosocomial pneumonia treated with aminoglycosides. Poor penetration into infected airways and in particular the alveoli, the site of bacterial multiplication in pneumonia, is considered to be one of the main causes of therapeutic failures with these agents.

Lung concentrations of aminoglycosides depend largely on the anatomic site sampled; thus, concentrations in the fluid lining the inner-alveolar surface (alveolar lining fluid [ALF]) cannot be predicted by concentrations in the whole lung tissue, bronchial secretions, and sputum. Adequate aminoglycoside concentrations, above the minimum inhibitory concentrations (MICs) of causative pathogens, in the alveolar compartment are required for clinical effectiveness. To date, few studies on aminoglycoside penetration of the alveolar acini and the fluid lining the inner-alveolar surface have been carried out.

The primary aim of the present study was to determine gentamicin concentrations in the serum and ALF of critically ill patients with ventilator-associated pneumonia (VAP) and to estimate the penetration ratio of this aminoglycoside in the ALF, so as to make useful suggestions regarding its therapeutic dosage regimens.

**Materials and Methods**

**Patients**

This open-labeled uncontrolled study took place at the University Intensive Care Unit of the “KAT” Hospital (Athens, Greece) after the study protocol was approved by the hospital scientific and ethics committee. Twenty-four, white, adult, intubated, critically ill patients receiving MV who were scheduled to undergo diagnostic fiberoptic bronchoscopy while receiving gentamicin for the treatment of VAP were selected for this study. All patients were admitted to the ICU for acute respiratory failure caused by exacerbation of COPD (n = 4), cerebrospinal injury (n = 4), multiple trauma (n = 5), cerebrovascular stroke (n = 9), heart failure (n = 1), and endocarditis (n = 1).

VAP diagnosis was based on a new and persistent infiltrate on the chest radiograph and two of the following three criteria: fever > 38.3°C, WBC count > 12,000/μL, and/or purulent tracheobronchial secretions. Patient exclusion criteria were allergy to gentamicin; aminoglycoside treatment < 7 days before bronchoscopy; abnormal renal function (serum creatinine > 1.6 mg/dL); contraindications to the BAL technique (refractory hypoxemia, unstable angina or recent acute myocardial infarction, hemodynamic instability, severe coagulopathy, or bleeding diathesis); BAL procedure duration > 2 min; and a lung injury score > 2, as defined by the scale of Murray et al. Informed consent was obtained from the nearest relative of all the patients.

**Drug Administration and Sampling Procedure**

Standard initial empiric treatment of VAP in our hospital ICU includes the administration of gentamicin and an extended spectrum β-lactam (e.g., piperacillin-tazobactam, ticarcillin-clavulanic acid, ceftazidime). Thus, all patients received a gentamicin IV infusion, 240 mg, over 30 min on the morning of the first treatment day (once-daily scheme). The gentamicin was diluted in 100 mL of normal 0.9% saline solution and administered through a central venous line.

All patients underwent fiberoptic bronchoscopy on the first treatment day with gentamicin. The 24 patients were assigned at random to one of four groups of 6 patients each according to the scheduled time for bronchoscopy. The six patients in these four groups underwent fiberoptic bronchoscopy 1, 2, 4, and 6 h, respectively, after the start of gentamicin infusion, and BAL fluid samples were collected from each patient.

BAL fluid samples were obtained using standard procedures. A flexible fiberoptic bronchoscope (Pentax FB-18P; Pentax, Tokyo, Japan) was inserted through the endotracheal tube and was wedged into a subdivision of a segmental bronchus of the right middle lobe, and the lavage was performed by infusing five 20-mL aliquots of sterile 0.9% saline solution through the aspiration port and withdrawing them immediately via the same port by gentle suction. The liquid recovered after the first aliquot was considered representative of a bronchial wash and was discarded, while the remaining lavage fluid was collected in sterile syringes and used for the determination of gentamicin concentrations. A small aliquot was sent to the microbiological laboratory for inspection as well. The time elapsed between the beginning of BAL and the total recovery of the five aliquots was always kept < 2 min to minimize free diffusion of solutes, particularly urea, through the alveolar epithelium that may lead to falsely elevated concentrations of urea in the BAL fluid. Urea was used as an endogenous reference marker and dilution factor for the calculation of gentamicin in the ALF because it diffuses readily through the various anatomic compartments of the body, including the anatomic barriers of the pulmonary alveolus. This means that urea exists at the same concentration in ALF as it does in the plasma, ie, urea (ALF) = urea (plasma). Blood samples of 5 mL each were obtained from all patients through a catheterized peripheral arterial line at the following scheduled time points: 0.5, 1, 2, 4, and 6 h after the start of IV gentamicin infusion.

**Sample Analysis**

Blood samples were centrifuged for 10 min at 3,500 revolutions per minute at 4°C, and serum was extracted from each sample, placed in plastic micro test tubes (Safe-Lock; Eppendorf AG; Hamburg, Germany), and immediately frozen at −70°C until analysis. BAL samples were centrifuged for 10 min at 3,500 revolutions per minute at 4°C; the supernatants were collected in plastic containers as were the blood samples and immediately frozen at −70°C until analysis.

Gentamicin concentrations in serum and in BAL fluid supernatant were determined using an automated fluorescence polarization method (TDx/FLx analyzer; Abbott Diagnostics; Abbott Park, IL). All reagents, calibrators, and controls of the analyzer were kept under controlled temperature conditions (2°C to 8°C), according to the instructions of the manufacturer.

In particular, gentamicin concentrations in the BAL fluid supernatant were determined according to the modified automated fluorescence polarization method of Govantes et al, which allows detection of very low aminoglycoside concentrations with a quantification limit of 0.02 μg/mL. The above method was validated in this study, giving coefficients of variation of 7.76%, 6.21%, and 4.61% for gentamicin concentrations of 0.025, 0.05, and 0.10 μg/mL, respectively. Analysis of all samples was performed in duplicate on the same day (batch processing) after the
analysed giving an accepted calibration curve with a root mean square error of 0.57.

Urea concentrations in serum and BAL fluid samples were determined using an enzymatic kinetic ultraviolet method (ABX Pentra CP kit; ABX Diagnostics; Montpellier, France) in a COBAS Mira Plus analyzer (ABX Diagnostics; Montpellier, France) according to the modification of Carcas et al16 with a quantification limit of 0.20 mg/dL.

Data Collection

The following data were collected, recorded, and/or calculated on an electronic spreadsheet: age, sex, body weight, height, gentamicin-administered dose, bronchoscopy randomization group, days on MV, body temperature (degrees Celsius), WBC count, BAL and ALF volumes, sampling times, blood and ALF gentamicin concentrations, serum creatinine, and creatinine clearance. The pharmacokinetic parameters of gentamicin (apparent distribution volume, elimination rate constant, clearance, and elimination half-life) for the 24 patients were calculated from serum concentrations by using a one-compartment pharmacokinetic model (WinNonlin v3.1 pharmacokinetic software; Pharsight Corporation; Cary, NC).

The anatomic site of pulmonary infection was recorded based on chest radiographs obtained the day of bronchoscopy. Respiratory function parameters were recorded from the mechanical ventilation devices before bronchoscopy: \( P_{aO_2} \), \( PCO_2 \), arterial pH, fraction of inspired oxygen (\( FIO_2 \)), respiratory frequency, tidal volume (\( V_T \)), and positive end-expiratory pressure (PEEP). Furthermore, the disease severity scores according to the APACHE (acute physiology and chronic health evaluation) II17 scale were calculated. The lung injury score was calculated according to the scale of Murray et al9 based on the anatomic location of alveolar consolidation on the chest radiograph and the values of \( P_{aO_2}/FIO_2 \), compliance, and PEEP.

Calculations

The apparent volume of ALF (\( V_{ALF} \)) was calculated using volume of BAL (\( V_{BAL} \)) according to the following equation12:

\[
V_{ALF} = V_{BAL} \times \frac{\text{urea (BAL)}}{\text{urea (ALF)}} \tag{1}
\]

As urea is a free low-molecular-weight substance that diffuses readily through the alveolar capillary membrane barrier, it may be assumed that urea (ALF) = urea (plasma). The gentamicin concentration (Gent) in the ALF was derived from the following equation:

\[
\text{Gent (ALF)} = \text{Gent (BAL)} \times \frac{V_{BAL}}{V_{ALF}} \tag{2}
\]

By combining equations 1 and 2, the gentamicin concentration in the ALF can be calculated as follows:

\[
\text{Gent (ALF)} = \text{Gent (BAL)} \times \frac{\text{urea (ALF)}}{\text{urea (BAL)}} \tag{3}
\]

which due to the assumption that urea (ALF) = urea (plasma) may be transformed into:

\[
\text{Gent (ALF)} = \text{Gent (BAL)} \times \frac{\text{urea (plasma)}}{\text{urea (BAL)}} \tag{4}
\]

The penetration ratio of gentamicin from blood to the ALF through the alveolar capillary membrane barrier was calculated from the ratio of the maximum gentamicin concentration in the ALF to the corresponding serum concentration.

Statistical Analysis

All data are expressed as mean ± SEM. For each patient, the age, weight, height, sampling time, gentamicin-administered dose, concentration of gentamicin and urea in serum and BAL fluid, fluid volumes, APACHE II score, lung injury score, body temperature, WBC count, and all respiratory function and pharmacokinetic parameters were defined as continuous variables, while the sex, the anatomic site of the pulmonary infection, and the kind of the biological sample (serum or BAL) were considered nominal variables.

Analysis of variance was used to compare the concentrations in serum and ALF at the four time periods. Prior to performing the analysis of variance, data sets were tested for normality (Wilk-Shapiro test) and equality of variances (Bartlett test). Parametric and nonparametric analyses were performed by the Neuman-Keuls and Kruskal-Wallis tests respectively.

The ALF/serum drug concentration ratios were calculated by averaging the ratios for the six subjects at each collection time point. The Spearman correlation test was used to evaluate the relation between gentamicin concentrations in the serum and ALF; \( p < 0.05 \) was considered statistically significant. Statistical processing and data analysis were performed using commercial software (SPSS 10.0; SPSS; Chicago, IL).

RESULTS

Twenty-four ICU patients (16 men and 8 women) were successfully enrolled in the study. However, three patients were dropped and replaced due to BAL sampling duration violations. All patients underwent a scheduled fiberoptic bronchoscopy the first day of treatment with gentamicin administered as an IV infusion of 240 mg (mean administered dose, 3.5 ± 0.1 mg/kg). All patients successfully completed the bronchoscopy and BAL procedures. No major adverse effects were noted except for a transient fall in arterial oxygen saturation in five patients.

The mean age of the patients was 63 ± 4 years (range, 24 to 92 years), the mean height was 170 ± 2 cm (range, 152 to 185 cm), and the mean weight was 71 ± 3 kg (range, 50 to 93 kg). Creatinine clearance, as a measure of renal function, was estimated for each patient from the serum creatinine concentrations using the equation of Cockroft and Gault,18 and ranged from 60.1 to 141.7 mL/min (mean, 103.9 ± 5.3 mL/min).

The mean value of gentamicin clearance in the blood was calculated as 117.9 ± 16.3 mL/min, and the mean elimination rate constant was 0.36 ± 0.04 h⁻¹, resulting in an elimination half-life of 2.6 ± 0.3 h. Also the mean gentamicin volume of distribution (apparent distribution volume) was found to be 0.30 ± 0.03 L/kg.

The average WBC count in patients blood was
14.371 ± 745/μL, and the mean maximum body temperature was 38.7 ± 0.1°C. The patients of the study underwent bronchoscopy 12.6 ± 2.2 days after admission to the ICU. The mean volume recovered from BAL was 31.5 ± 1.5 mL, while the mean quantified apparent ALF volume was 0.5 ± 0.1 mL.

According to chest radiographs, the majority of patients (79.2%) exhibited pulmonary infiltrations at the lung bases, while only in a small percentage (20.8%) lung apexes were involved in the pulmonary infection as well. The anatomic site of pulmonary infection on the day of bronchoscopy for all the patients of the study is shown in Table 1.

The mean values of respiratory function parameters and other baseline parameters prior to bronchoscopy are presented in Table 2. Mean gentamicin concentrations achieved in serum and ALF as a function of time from the initiation of gentamicin infusion are shown in Figure 1. The mean maximum gentamicin concentration (Cmax) in serum (13.39 ± 0.91 μg/mL) occurred 0.5 h after the start of gentamicin infusion, while the mean Cmax in ALF (4.24 ± 0.42 μg/mL) was observed after 2 h. Maximum/minimum mean serum and ALF concentration ratios were 3.54 and 1.60, respectively. The ratio of the mean Cmax in ALF to that in serum (Cmax [ALF]/Cmax [serum]) was 0.32 (a penetration ratio of 32%).

The mean ratios of ALF to serum concentrations of gentamicin were 0.30 ± 0.05 at 1 h, 0.85 ± 0.10 at 2 h, 1.14 ± 0.26 at 4 h, and 0.74 ± 0.18 at 6 h. A significant (p = 0.007) difference among the gentamicin ALF/serum concentration ratios at the four time periods was found. The mean gentamicin ALF/serum ratio at 1 h was significantly higher than that at 2 h (p < 0.05) and 4 h (p < 0.01). A statistically significant positive correlation (r = 0.54, p = 0.02) was found between gentamicin concentrations in serum and ALF after completion of the distribution phase in the ALF, i.e., after the peak concentration.

### Table 1—Anatomic Site of Pulmonary Infection in Study Patients*

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLL</td>
<td>8 (33.33)</td>
</tr>
<tr>
<td>LLL and LRL</td>
<td>7 (29.17)</td>
</tr>
<tr>
<td>LRL</td>
<td>4 (16.67)</td>
</tr>
<tr>
<td>URL and LRL</td>
<td>2 (8.33)</td>
</tr>
<tr>
<td>LLL and URL</td>
<td>2 (8.33)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (100)</td>
</tr>
</tbody>
</table>

*L = lower lobe; U = upper lobe; LRL = lower right lobe.

### Table 2—Patient Respiratory Function and Other Baseline Parameters Prior to Bronchoscopy*

<table>
<thead>
<tr>
<th>Parameters Recorded</th>
<th>All Patients (n = 24)</th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 6)</th>
<th>Group 3 (n = 6)</th>
<th>Group 4 (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>107.4 ± 7.8</td>
<td>124.0 ± 26.8</td>
<td>108 ± 18.0</td>
<td>97.5 ± 9.3</td>
<td>105.7 ± 13.0</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>37.7 ± 1.3</td>
<td>38.5 ± 3.8</td>
<td>38.5 ± 3.2</td>
<td>37.7 ± 2.0</td>
<td>36.2 ± 2.6</td>
</tr>
<tr>
<td>PaO₂/FIO₂, mm Hg</td>
<td>225.2 ± 23.5</td>
<td>279.3 ± 80.3</td>
<td>230.2 ± 46.8</td>
<td>179.8 ± 23.5</td>
<td>229.5 ± 48.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.41 ± 0.02</td>
<td>7.39 ± 0.02</td>
<td>7.43 ± 0.02</td>
<td>7.42 ± 0.02</td>
</tr>
<tr>
<td>MV (assist-control ventilation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>14.8 ± 0.8</td>
<td>16.5 ± 2.0</td>
<td>15.7 ± 1.5</td>
<td>14.2 ± 1.6</td>
<td>13.5 ± 1.3</td>
</tr>
<tr>
<td>VT, mL</td>
<td>498.6 ± 10.5</td>
<td>517.5 ± 11.8</td>
<td>481.7 ± 9.8</td>
<td>506.7 ± 23.6</td>
<td>495.0 ± 29.2</td>
</tr>
<tr>
<td>PEEP, cm H₂O</td>
<td>2.6 ± 0.5</td>
<td>1.8 ± 1.2</td>
<td>3.0 ± 1.0</td>
<td>3.2 ± 1.0</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td>Compliance</td>
<td>37.3 ± 3.8</td>
<td>30.8 ± 1.4</td>
<td>30.3 ± 5.2</td>
<td>47 ± 5.3</td>
<td>43.3 ± 6.4</td>
</tr>
<tr>
<td>Days receiving MV</td>
<td>12.6 ± 2.2</td>
<td>13.2 ± 6.4</td>
<td>14.7 ± 3.9</td>
<td>13.4 ± 5.3</td>
<td>9.5 ± 2.9</td>
</tr>
<tr>
<td>Severity scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung injury score</td>
<td>1.4 ± 0.1</td>
<td>1.5 ± 0.3</td>
<td>1.4 ± 0.1</td>
<td>1.5 ± 0.2</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19.1 ± 0.9</td>
<td>20.3 ± 1.9</td>
<td>17.3 ± 1.9</td>
<td>18.0 ± 2.3</td>
<td>21.0 ± 0.7</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM. No statistically significant differences in mean values of respiratory function and other baseline parameters were observed among the four groups (p > 0.05).
Discussion

In the present study, gentamicin penetration of ALF was assessed by comparing concentrations of the antibiotic achieved in the ALF and serum following the IV administration of a once-daily dosing schedule in 24 critically ill patients with VAP. As far as we are aware from the literature (MEDLINE search, key words “gentamicin,” “BAL,” “bronchoalveolar lavage,” “alveolar lining fluid”), this is the first human study in which gentamicin concentrations have been compared in these two compartments. The BAL technique allows collection of samples from ALF and the determination of antibiotic concentrations in the samples.19–21 To date, few studies have been performed to determine aminoglycoside concentrations (eg, netilmicin,22 tobramycin16,23) in BAL fluid following administration of these antimicrobial agents.

Clinical effectiveness of aminoglycosides is strongly correlated to the ratio of their Cmax serum to the MIC of causative pathogens.24–26 More specifically a Cmax serum/MIC ratio of > 8:1 to 10:1 is required to achieve clinical response in > 90% of cases to optimize bactericidal activity and to avoid bacterial regrowth of pathogenic microorganisms.24,27 However, previous studies25,27 mentioned that it is not definitely known whether high blood concentrations of aminoglycosides will also lead to high concentrations in the alveolar compartment of patients with pneumonia. Antibiotic penetration of the respiratory tract is influenced by alterations in the permeability of certain anatomical barriers of the lung, by the physicochemical properties of these drugs, and by their inactivation due to changes in local pH, anaerobic conditions, or enzyme activity.4,28,29 Moreover, aminoglycoside concentrations measured in the lung depend to a great extent on the anatomic site of sample collection. Reports in the literature have referred to aminoglycoside concentrations in the whole lung tissue, sputum, and bronchial secretions approximately 50%, 20 to 60%, and 20%, respectively, of serum levels.5–7 Taking into account all the above, measurement of aminoglycoside concentrations at the actual site of the respiratory infection, ie, the acini and the surrounding alveolar fluid, is considered to be more relevant.

Gentamicin concentrations in the ALF were determined by performing BAL.10,11 Although the volume of BAL fluid injected during the procedure has not been standardized, the volumes used in studies on critically ill patients ranged from 100 to 300 mL.50 In order to minimize complications from the procedure in the critically ill patients of our study, we chose to inject a total of 100 mL of normal saline.
solution divided into five smaller aliquots of 20 mL. During this procedure, the fluid lining the surface of the lung is diluted by the solution instilled into the airways. To overcome this dilutional effect, the concentration of a solute, such as urea (introduced by Rennard et al12) normally present at the same concentrations in the blood and ALF is measured. Although urea is used as a dilution marker, it is not considered ideal, as it appears that urea from sources other than the recovered ALF is likely to diffuse into the recovered lavage fluid during the lavage procedure. This results in falsely elevated urea concentrations in the BAL fluid, an overestimation of the ALF volume, and subsequent underestimation of the drug concentration.11,12,31 The problem may be worsened if the duration of the BAL procedure is increased or if the permeability of the alveolar membrane is increased through injury. For this reason, patients with overt clinical pulmonary abnormalities, such as ARDS or lung injury scores of > 2 (Murray et al36 scale) were excluded from the study, and the instillation and recovery of fluid was completed in < 2 min.

Penetration of gentamicin and aminoglycosides through the anatomic barriers of the body is generally poor. Recently, it has been found that gentamicin penetration of the blood-retinal barrier is difficult even when high serum levels are achieved after once-daily dosing.32 While different ocular diseases do not alter the ocular barrier substantially.33 Moreover, aminoglycoside penetration through the intact blood-cerebrospinal fluid barrier is also very low, giving penetration ratios of, for example, 0.004 to 0.025 for netilmicin.34 These have been found to slightly increase in patients with meningitis.35 Penetration of aminoglycosides into the breast milk is limited. A study36 with gentamicin found milk-to-plasma penetration ratios between 0.11 and 0.44 at 1 h and 7 h after drug administration, respectively. In contrast, the aminoglycosides easily penetrate the placental barrier, and fetal serum concentrations ranging from 21 to 37% of maternal serum concentrations have been reported.37,38

Drug penetration of lung tissue is increased by the inflammation associated with bacterial infection, which is characterized by increased blood perfusion, vascular dilatation, increased vascular permeability, and the production of an exudate rich in proteins and inflammatory cells.4,28 In the study of Valcè et al,39 the penetration of gentamicin and tobramycin into the ALF of rats following airway inflammation (caused by an inhaled endotoxin) was found to be increased, in particular for gentamicin, with or without the presence of inflammation. As previously mentioned, the penetration ratio of gentamicin in the present study was 0.32, while the ALF/serum concentration ratios 1 to 6 h following administration ranged from 0.30 to 1.14. Similarly, in a study16 of 16 ICU patients with pneumonia who received tobramycin IV every 8 h (the actual dose given was not stated), the ratio of peak ALF/serum concentrations was approximately 0.32, while the ratio of these concentrations 1 to 8 h following administration ranged from 0.30 to 1.53. Also, in another study by Braude et al,23 where nine patients with various respiratory diseases were treated with IV tobramycin, 1 to 1.7 mg/kg, the ratio of ALF/serum concentrations 10 h after administration was 0.5 (using creatinine and not urea as a dilution marker). In contrast, Mazzei et al40 found higher concentrations of tobramycin in the ALF compared with the serum 6 h after administration of two different IM bolus doses of 150 mg or 300 mg to 10 critically ill patients, giving ratios of ALF/serum of 1.4 and 1.6, respectively.

In the study of Valcke et al22 of 20 ICU patients with pneumonia to whom an IV once-daily standard dose of 450 mg netilmicin was infused, the peak antibiotic concentration in the ALF was 41% of the corresponding concentration in plasma, and the ratio of ALF/plasma concentrations ranged from 0.35 to 1.12, 1 to 3 h after initiation of therapy. The time required to achieve peak netilmicin concentrations in the ALF was 2 h, similar to that found for gentamicin in the present study, and this period may be considered characteristic for most of the aminoglycosides after once-daily dosing, but this finding must be confirmed with further study.

Mean gentamicin concentrations in the ALF fluid appear to correlate with concentrations in the serum after the distribution phase in the ALF. Thus, gentamicin distributes into the alveolar compartment in a concentration dependent on blood levels. This is in agreement with the concept that antimicrobial agents transfer across the alveolar-capillary membrane by passive concentration dependent diffusion.28 Positive correlations between ALF and serum levels were also found in the study of Braude et al23 and Carcas et al16 on tobramycin. At the end of the dosage interval, ie, 8 h in the study of Carcas et al,16 the mean ALF/serum ratio was 1.53, indicating accumulation of the antibiotic in the alveoli of pneumatic areas. According to these authors,16 their finding supports the theory that the ALF behaves as a deep compartment and not as extracellular fluid.

Resolution of laboratory and clinical response variables such as WBC count, body temperature, sputum production, and purulence combined with a marked improvement in the chest radiograph findings after 7 days of therapy indicated that VAP in all study patients was successfully treated. Gentamicin MICs of common pathogens isolated in our ICU
(Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Klebsiella spp, Enterobacter spp, Proteus spp, Acinetobacter spp) range from 1 to 4 µg/mL. Kashuba et al.\(^4\) reported that a Cmax/MIC serum ratio > 4.7 within 48 h of initiation of aminoglycoside therapy in patients with nosocomial pneumonia results in a temperature resolution success rate of 89% and a leukocyte count resolution success rate of 86% after 7 days of therapy. Thus, the once-daily dosing schedule and concomitant administration of other antibiotics in our study probably contributed to resolution of VAP in the 24 study patients, but for the less sensitive pathogens that did not satisfy this ratio, the administration of a higher gentamicin dose would have been more appropriate. The successful treatment of VAP in our study patients is encouraging in view of the gentamicin concentrations found in the ALF. This may suggest that a lower Cmax/MIC ALF ratio is required for the best possible therapeutic response with aminoglycoside therapy for pneumonia. As the optimal ratio in the ALF is not known, a similar study to that of Kashuba et al.,\(^4\) but studying the Cmax/MIC ALF ratio after once-daily administration of aminoglycosides, would provide valuable information with regard to possible success rates in patients with nosocomial pneumonia; this could be the target of a future research protocol.

**Conclusions**

Once-daily, IV administration of gentamicin, 240 mg, achieved average peak antibiotic concentrations of 4.24 µg/mL in the ALF 2 h after administration and an adequate ALF-serum penetration ratio of 32%. However, a gentamicin dose higher than the study dose is necessary to obtain active alveolar concentrations against less-sensitive microorganisms in the treatment of VAP in ICU patients.

**Acknowledgment:** We thank Dr. Evangelia Kouskouni, Head of the Microbiology Department, Aretaieion Hospital (Athens, Greece) for her kind assistance in the laboratory.

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www.chestjournal.org CHEST / 128/2 / AUGUST, 2005 551