Pulmonary Disposition of Vancomycin in Critically Ill Patients

H. Georges[1]*, O. Leroy[1], S. Alfandari[1], B. Guery[1], M. Roussel-Delvallez[2], C. Dhennain[3], G. Beaucaire[1]

Vancomycin penetration in epithelium lining fluid was studied in ten mechanically ventilated patients with methicillin-resistant *Staphylococcus aureus* pneumonia 24 hours after the onset of treatment. Vancomycin was given intravenously at a daily dose of 30 mg/kg. Vancomycin levels were detectable in four patients (range, 1–2.77 μg/ml). Concordance between high plasma concentrations (> 20 μg/ml) and detectable vancomycin levels in epithelium lining fluid was noted. These results suggest that the pulmonary disposition of vancomycin remains low for most patients 24 h after the onset of treatment compared with the minimum inhibitory concentrations for most gram-positive organisms. One therapeutic goal of vancomycin treatment could be to obtain through plasma levels of 20 μg/ml. Further studies are required to determine the clinical relevance of these observations.

Successful treatment of bacterial pneumonia depends on adequate delivery of antibiotic to the infected area. Vancomycin is often the only antibiotic available to manage pneumonia due to methicillin-resistant *Staphylococcus aureus* (1), yet there is a lack of data on vancomycin distribution in lung tissue, especially at the onset of treatment. Many procedures are available to determine pulmonary disposition of antimicrobial agents. Among these, determination of antibiotic levels in epithelium lining fluid (ELF) seems to be an easy and reliable method (2). The aim of the present study was to investigate the pulmonary disposition of vancomycin in mechanically ventilated patients with *Staphylococcus aureus* bronchopneumonia 24 hours after the onset of treatment.

Materials and Methods. The present study was conducted prospectively between January 1994 and October 1994 in a 16-bed medical/surgical ICU. The study population consisted of ten mechanically ventilated patients with bronchopneumonia due to methicillin-resistant *Staphylococcus aureus*. There were six males and four females with a mean age of 65.5 ± 8.4 years. Informed consent was obtained from all patients or from the nearest relative. The study was approved by the Lille Medical University's Ethics Committee.

Patients were admitted for acute respiratory failure caused by exacerbation of chronic obstructive pulmonary disease (COPD) (n = 4), community-acquired pneumonia (n = 3), cerebral hemorrhage (n = 1), meningitis (n = 1), or pulmonary embolism (n = 1). Weights ranged from 51 to 97 kg (mean, 72 ± 11 kg). Coexisting diseases were COPD (5 patients), cirrhosis (1 patient), and malignancies (2 patients). At the onset of *Staphylococcus aureus* bronchopneumonia, the mean duration of mechanical ventilation was 10.6 ± 3.9 days. *Staphylococcus aureus* bronchopneumonia caused sepsis syndrome in eight patients and septic shock in two patients. No surgical procedure was performed on any patient during the ICU stay. Four patients received steroids during the study period, and nine patients received antibiotics other than vancomycin.

Staphylococcus aureus bronchopneumonia was defined by hyperthermia of ≥ 38.3°C, leukocytosis of ≥ 12 x 10^9/l, new and progressive infiltrates on chest radiograph, purulent tracheal secretions, and a protective specimen brush sample positive for *Staphylococcus aureus* (≥ 10^3 cfu/ml). Serum creatinine level was < 14 mg/l for all patients. No patient had previously received vancomycin or another glycopeptide within seven days of entry into the study. Vancomycin was given intravenously at a daily dose of 30 mg/kg in four equal discontinuous infusions administered for a 1 h period every 6 h.

Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) was performed 24 h after the onset of treatment, just before the next planned infusion of vancomycin, to obtain ELF. Bronchoalveolar lavage was performed into a subsegmental airway of the middle lobe or lingula by infusing five 20 ml aliquots of sterile 0.9% saline solution

[1]Service Universitaire de Réanimation Médicale et Maladies Infectieuses, and [3]Laboratoire de Bacteriologie, Hôpital Chatilliez, 135 rue du Président Coty, 59208 Tourcoing, France.
[2]Laboratoire de Bacteriologie, Hôpital A. Calmette, Lille University Medical School, France.

Table 1: Levels of urea, albumin, and vancomycin in plasma, bronchoalveolar lavage (BAL) fluid, and epithelium lining fluid (ELF) of the ten patients.

Patient no.	BAL fluid recovered (ml)	Urea in plasma (g/l)	Urea in BAL fluid (mg/dl)	Albumin in BAL fluid (mg/dl)	ELF recovered (ml)	Vancomycin in plasma (μg/ml)	Lyophilized vancomycin (μg/ml)	Vancomycin in ELF (μg/ml)	Albumin in ELF (mg/ml)
1	55	0.62	0.98	4.5	0.86	18.1	<0.5	–	5.23
2	43	0.51	0.86	0.4	0.72	22.5	1	1.38	0.55
3	9	0.3	0.7	0.12	0.21	14.6	<0.5	–	0.57
4	29	0.47	0.96	2.7	0.59	22.1	1.2	2.03	4.57
5	27	0.4	1.2	1.4	0.81	13.2	<0.5	–	1.72
6	50	0.78	2.6	7.6	1.66	23.2	4.6	2.77	4.57
7	27	0.86	1.8	1.87	0.56	20.9	1.04	1.95	3.35
8	25	0.27	0.52	0.81	0.48	8.4	<0.5	–	1.68
9	35	0.22	0.66	0.6	1.05	7.7	<0.5	–	0.57
10	32	0.34	1.2	2.4	1.12	12.4	<0.5	–	2.14
Mean ± SD	33.9±14.1	0.47±0.21	1.14±0.62	2.24±2.29	0.8±0.38	16.3±5.8			2.49±1.8

through the aspiration port and withdrawing them immediately via the same port by gentle suction. Time elapsed between beginning of BAL and recovery of the five aliquots was < 2 min. Liquid recovered after infusion of the first aliquot was considered representative of a bronchial wash and was discarded. To investigate plasma vancomycin concentrations, blood samples were withdrawn at the end of the bronchoscopy procedure.

Recovered BAL fluids were poured through a gauze, and an aliquot was submitted for cytologic examination prior to any centrifugation. The remaining fluid was centrifuged for 5 min to separate cells from the fluid component. Wright-Giemsa stain smears served to identify differential profiles after cytospin preparation. Bronchial epithelial cells were counted and recorded as the percentage of total cells. Fluid supernatant was stored at −70°C until analyzed. Albumin concentration in plasma and BAL fluid was determined by enzyme immunoassay to quantify parenchymal lung inflammation (3).

To quantify the volume of ELF in fluid supernatant recovered, urea was used as an endogenous marker of ELF, since urea diffuses throughout the alveolar wall (4). As urea concentrations in ELF and plasma are the same, the volume recovered can be calculated if the plasma urea concentration and the quantity of urea in a lavage sample are known: [volume of recovered BAL (ml) x concentration of urea in BAL (mg/ml)] concentration of urea in plasma (mg/ml).

To determine the urea content of lavage fluid samples, a commercially available kit (Sigma 65-UV; Sigma Diagnostics, USA) was used.

An aliquot of BAL fluid supernatant was lyophilized and the powder suspended in 1 ml of 10^{-3} ml of hydrochloric acid. The concentration of vancomycin in suspension was then determined by a fluorescence polarization immunoassay (TDX; Abbott Laboratories, UK). The limit of detection of vancomycin in suspension was 0.5 μg/ml. The vancomycin concentration was then matched to the volume of ELF obtained by BAL.

Exclusion criteria were as follows: patients with severe pulmonary disorders as defined by a Murray score of > 2.5 (5); proportion of bronchial epithelial cells in BAL fluid > 2% of total cells; BAL procedure duration > 2 min; erythrocyte contamination with > 5 cells/oil-immersion field.

Data were expressed as means ± standard deviations. Statistical methods used the independent Student's t-test.

Results and Discussion. Bronchoalveolar lavage was performed safely in all patients; none was excluded from the study. Volume recovered from BAL was 33.9 ± 14.1 ml, with a mean cell count of 262 x 10^3/ml of lavage fluid. Recovery was poor in one patient (no. 3) because of preexisting COPD. The differential cell count revealed 40% ± 34% macrophages, 55% ± 28% neutrophils, and 5% ± 4% lymphocytes. The calculated volume of ELF recovered from lavage averaged 0.8 ± 0.38 ml. The albumin concentration in ELF was calculated to be 2.46 ± 1.54 mg/ml. Vancomycin levels in lyophilized suspension were detectable in only four patients (Table 1). In these patients the mean vancomycin concentration matched to ELF was 2.03 ± 0.49 μg/ml (range, 1 to 2.77 μg/ml) and the mean simultaneous level in plasma 22.19 ± 0.83 μg/ml. Vancomycin in

ELF was undetectable in six patients. For these patients the mean simultaneous level in plasma was 12.45 ± 3.56 μg/ml. There was no difference between the two groups regarding parenchymal lung inflammation.

Vancomycin is usually considered the first-line agent for treatment of MRSA bronchopneumonia, yet little is known about its pulmonary disposition. Recently, Lamer et al. (3) demonstrated that vancomycin was distributed in the pulmonary ELF at a concentration dependent on blood levels and alveolar capillary membrane permeability when it was administered for at least five days.

Epithelium lining fluid, considered an important site of infection in pneumonia, is the fluid that lines the small distal airways. In our study we chose to perform a rapid lavage technique (instillation and collection procedures required < 2 min) to avoid an overestimation of ELF volume (4). In the same way, to circumvent permeability of pulmonary epithelium due to clinical injuries, patients with pulmonary disorders defined by a Murray score of > 2.5 were excluded (5).

In our study, vancomycin levels in ELF 24 h after the onset of administration were lower for most patients than the minimum inhibitory concentrations (MICs) for most gram-positive organisms (0.25–2 μg/ml) (6) and the NCCLS breakpoint concentration recommended for vancomycin (4–32 μg/ml) (7). Indeed, vancomycin levels in lyophilized suspension were below the assay sensitivity limit (0.5 μg/ml) in six patients. Discrepancies between plasma and ELF levels can be explained by significant variations in distribution and excretion of vancomycin, both of which are influenced by age, sex, volume of distribution, and body weight (8).

We chose to perform BAL at times of trough concentrations because optimal vancomycin therapy requires sustained therapeutic concentrations and does not require peaks (9). Our samplings were performed 24 h after the onset of treatment. This could be premature; it may be necessary to perform BAL later to assess the pulmonary disposition of vancomycin, since vancomycin levels in ELF are stable five days after the onset of treatment (3).

A striking point of our study is the concordance between high trough concentrations of vancomycin in serum and vancomycin levels in ELF. Indeed, all four patients with vancomycin levels in ELF had trough plasma concentrations above 20 μg/ml. By contrast, all six patients with undetermined levels in ELF had plasma concentrations below 20 μg/ml. These data have already been suggested by Lamer et al. (3): after five days of administration, vancomycin levels in ELF were two to 30 times the MICs for most gram-positive organisms in patients with plasma levels above 20 μg/ml. These authors were able to detect vancomycin in ELF in a few patients with plasma levels of < 20 μg/ml. However, the duration of vancomycin administration before sampling was different (5 days vs. 1 day in our study); effective distribution of vancomycin in lung parenchyma is slow, and tissue levels are generally superior to plasma levels after a few days (10).

Therefore, one therapeutic goal of vancomycin administration in patients with severe *Staphylococcus aureus* pneumonia could be to achieve vancomycin trough levels of at least 20 μg/ml in plasma. These high trough levels of vancomycin are not those currently recommended (troughs of 5 to 10 μg/ml). However, many studies have demonstrated little or no toxicity with vancomycin therapy (11, 12), and the largest study of treatment-associated toxicity showed a 3% incidence of reversible renal impairment in patients whose trough levels ranged from 30 to 65 mg/l with correspondingly elevated peaks (13). Pharmacodynamics studies could be conducted to determine the efficacy of high trough levels at the onset of treatment, particularly when *Staphylococcus aureus* is sensitive only to glycopeptides. To our knowledge, there is no controlled trial in which pulmonary and plasma vancomycin concentrations have been related to clinical response.

In summary, discrepancies in vancomycin levels in lung tissue appear 24 h after the onset of treatment. Plasma vancomycin trough levels of at least 20 μg/ml appear necessary to achieve satisfactory levels in lung tissue. Nevertheless, the clinical significance of antibiotic levels in ELF in terms of outcome of treatment for pneumonia is unknown. Controlled trials relating plasma and ELF concentrations to clinical response are necessary.

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Etiology and Response to Antibiotic Therapy of Community-Acquired Pneumonia in French Children

D. Gendrel*, J. Raymond, F. Moulin, J.L. Iniguez, S. Ravilly, F. Habib, P. Lebon, G. Kalifa

The aim of this study was to determine the etiologic agents associated with community-acquired pneumonia in 104 French children ages 18 months to 13 years. Potential respiratory pathogens were identified in 87 (85%) cases; these included respiratory syncytial virus in ten, other viruses in 20, *Streptococcus pneumoniae* in 14, and *Mycoplasma pneumoniae* (diagnosed by serologic procedures) in 43. Of 32 patients with *Mycoplasma pneumoniae* infection who were initially treated with beta-lactam antibiotics, 30 failed treatment. Recovery from mycoplasma infection occurred rapidly in patients treated with macrolide antibiotics (which included spiramycin in 31 patients, josamycin in 7, and erythromycin in 3); however, cough persisted in 12 patients for one month. The high frequency of *Mycoplasma pneumoniae* infection in community-acquired pneumonia in children over 18 months of age must be considered when selecting an antibiotic for initial therapy.

Antibiotic treatment of pneumonia in children is often empirical, since determination of the etiologic agents is difficult and is rarely performed in this age group (1–6). The incidence of the different pathogens involved in community-acquired pneumonia is suspected to vary. Penicillin resistance in *Streptococcus pneumoniae*, an important cause of pneumonia in children, is increasing rapidly. In addition, some studies have reported a high frequency of *Mycoplasma pneumoniae* in lower respiratory tract infections in children. In contrast, widespread immunization with the *Haemophilus*

Hôpital Saint Vincent de Paul, 82 Avenue Denfert-Rochereau, 75014 Paris, France.