Effectiveness of Cephalosporins in the Sputum of Patients with Nosocomial Bronchopneumonia

Almos Klekner,1* Kinga Bagyi, 2 Laszlo Bognar,1 Attila Gaspar,3 Melinda Andrasi, 3 and Judit Szabo 4

Department of Neurosurgery, Medical and Health Science Center, University of Debrecen, Nagyerdei krt. 98, 4012 Debrecen, Hungary1; Faculty of Dentistry, Medical and Health Science Center, University of Debrecen, Nagyerdei krt. 98, 4012 Debrecen, Hungary2; Department of Inorganic and Analytical Chemistry, University of Debrecen, Nagyerdei krt. 98, 4012 Debrecen, Hungary3; and Institute of Medical Microbiology, Medical and Health Science Center, University of Debrecen, Nagyerdei krt. 98, 4012 Debrecen, Hungary4

Received 28 April 2006/Returned for modification 3 May 2006/Accepted 31 May 2006

Nosocomial bronchopneumonia is a frequent complication in patients with chronic intratracheal intubation. Despite targeted antibiotic treatment, production of abundant bronchial secretion containing pathogenic bacteria often tends to be chronic, and so mortality drastically increases. This problem led to an investigation of the penetration of five cephalosporin antibiotics into the sputum. Serum and sputum were collected from 24 chronically intubated patients having purulent nosocomial bronchopneumonia treated in an intensive care unit (ICU). Patients received the following doses intravenously every 24 h: five received 70 mg/kg of body weight cefuroxime, four received 110 mg/kg cefamandole, six received 80 mg/kg ceftriaxone, four received 80 mg/kg ceftazidime, and five received 80 mg/kg cefepime. Antibiotic concentrations in the serum and sputum were evaluated by capillary electrophoresis. MICs were determined for bacteria isolated from the purulent bronchial secretions. The mean levels of the cephalosporins in the sputum did not reach the MICs for the bacteria isolated from the same samples. Ceftriaxone was the only one of the investigated five cephalosporins that had a measurable concentration in the sputum (1.4 ± 1.2 μg/liter). The low concentration of antibiotics in the purulent tracheobronchial secretion can be one of the many reasons for ineffective therapy of nosocomial bronchopneumonia in intubated patients in the ICUs. In the case of intubated or mechanically ventilated patients having chronic bronchopneumonia, determination of drug concentration in the bronchial secretion might be considered when selecting an antibiotic for treatment.

* Corresponding author. Mailing address: Department of Neurosurgery, MHSC, University of Debrecen, Nagyerdei krt. 98, 4012 Debrecen, Hungary. Phone and fax: 36-52-419-418. E-mail: aklekner@yahoo.com.
before use, the capillaries were preconditioned with methanol at 270 nm. The electropherograms were recorded and detection was carried out by on-column photometric measurement. The temperature of the capillary holder was kept constant at 25°C. A capillary length of 40 cm was used for injecting samples. The sample solutions were introduced at the anodic end of the capillary. Separations were performed using fused-silica capillaries coated on the outside with polyimide (Polymicro Technology, Phoenix, AZ). Capillaries were prepared on the day before inoculation. Each well was inoculated with a 1.5 × 10⁵ CFU per ml bacterial suspension. Thus, the final inoculum was 10 μl bacterial suspension. The stock solutions were stored at 4°C for a maximum of 24 h. The inoculum was prepared as follows. Isolated colonies from blood agar were grown in Mueller-Hinton broth (Oxoid) for 18 h at 37°C. The strains were diluted in Mueller-Hinton broth to yield an inoculum of 1.5 × 10⁶ CFU per ml. The stock solutions of antibiotics were serially twofold diluted in Mueller-Hinton broth to obtain working concentrations of 0.016, 0.032, 0.064, 0.128, 0.25, 1.0, 2.0, 4.0, 8.0, 16.0, 32.0, and 64.0 μg/ml. Ninety-microliter amounts from broth containing twofold concentration increments of antimicrobial agents were added to 96-well microdilution trays. In general, the plate was prepared on the day before inoculation. Each well was inoculated with 10 μl bacterial suspension. Thus, the final inoculum was 1.5 × 10⁴ CFU/ml. The strains were also inoculated on antibiotic-free control plates. Growth (turbidity) of aerobic strains was recorded after 18 h at 37°C. The MIC was reported as the lowest concentration of the antibiotic at which no growth was recorded (34).

**Observations.** The concentrations of the cephalosporins in the serum 6 hours after intravenous drug administration were as follows: cefuroxime, 26.9 ± 4.9 mg/liter; cefamandole, 41.5 ± 10.6 mg/liter; ceftazidime, 9.1 ± 2.0 mg/liter; ceftriaxone, 64.8 ± 20.8 mg/liter; and cefepime, 28.2 ± 25.3 mg/liter.

The levels of cefuroxime, cefamandole, ceftazidime, and cefepime in the sputum remained under 0.5 mg/liter, but the concentration of ceftriaxone was 1.4 ± 1.2 mg/liter (Table 1).

### Table 1. Mean concentrations of five cephalosporins in the serum and sputum 6 hours after intravenous drug administration

<table>
<thead>
<tr>
<th>Cephalosporin</th>
<th>No. of cases</th>
<th>Mean concn (mg/liter) ± SD in:</th>
<th>Serum</th>
<th>Sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime</td>
<td>5</td>
<td>26.9 ± 4.9</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>Cefamandole</td>
<td>4</td>
<td>41.5 ± 10.6</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>6</td>
<td>64.8 ± 20.8</td>
<td>1.4 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>4</td>
<td>9.1 ± 2</td>
<td>&lt;0.5</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>5</td>
<td>28.2 ± 25.3</td>
<td>&lt;0.5</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. MICs for nine bacterial strains from sputum of five cephalosporins

<table>
<thead>
<tr>
<th>Bacterial species</th>
<th>No. of cases</th>
<th>MIC (mg/liter) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>2</td>
<td>64</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3</td>
<td>1,024</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
Nine bacterial strains were isolated from the sputum cultures of the investigated 24 patients. In 10 cases, two bacteria were found in the tracheobronchial secretion. The results of the MICs for the bacteria are detailed in Table 2. The MICs of the investigated five cephalosporins exceed the mean concentrations of cephalosporins in the sputum. In two cases, the level of ceftriaxone in the sputum was higher than 2.0 mg/liter (2.2 and 3.8 mg/liter), which is theoretically high enough for treating six of the nine bacterial strains, but in both cases MICs for the bacteria were over 4 mg/liter (Acinetobacter baumannii and Staphylococcus aureus).

**Discussion.** Medicinal treatment of bronchopneumonia for chronically intubated patients in intensive care units always means a considerable effort for the clinicians (12, 19, 23). Pulmonary complications in unconscious patients in neurosurgical ICU can also decrease the chances for a satisfactory outcome (15, 31). If production of purulent bronchial secretion becomes chronic in spite of the antibacterial therapy, the likelihood of developing polyresistant bacterial strains increases. Nosocomial infections especially impede treatment, although there are some therapeutic guidelines in the literature (3–5, 28, 39).

The therapeutic benefits of the different cephalosporins have been often described, and their wide spectrum of effectiveness often distinguishes them among the chosen antibiotics (11, 26–28). Cefuroxime (6, 18), cefmamandole (38), ceftriaxone (20, 25, 35), ceftazidime (3, 11, 37), and cefepime (5) also are recommended antibiotics for treating pneumonia. The abundant bronchial secretion from purulent bronchopneumonia in chronically intubated comatose patients serves as a suitable medium for bacteria, which makes therapy many times more difficult. Some tests of the antibiotic concentrations in sputum have already been carried out (10, 20, 25, 35, 37). Although antibiotics could be detected in the majority of the measurements, the concentration of the investigated drug did not always reach the MIC of the bacterial strains found in the samples (6). In some other studies, the determined drug levels were low (1, 18, 25), but there are reports of appropriate antibiotic concentration in the sputum, too (2, 11, 30, 37). In consideration of the wide spectrum of the reported results and the low number of measurements directly in purulent secretion, further pharmacodynamical investigations are still needed.

The high mortality rate and the long-lasting treatment period for patients with nosocomial bronchopneumonia despite the specified antibiotic therapy led to the investigation of the presence of antibiotics in bronchial secretions after intravenous drug administration. The level of antibiotics in serum corresponded to the reported results in the literature, but only the mean concentration of ceftriaxone exceeded the 0.5-mg/liter detectability level in the sputum while cefuroxime, cefamandole, ceftazidime, and cefepime remained under this level, and the mean concentrations of all investigated antibiotics did not reach the MICs for the bacteria isolated from the purulent bronchial secretion (Tables 1 and 2).

**Conclusions.** In spite of the targeted treatment based on the culture from the copious sputum from nosocomial bronchopneumonia in intubated comatose patients, the therapy seems to be often ineffective. One of the main reasons for this clinical experience can be the low concentrations of the drugs—in this case five cephalosporins—in the purulent bronchial secretion. The fast and economical method for detection of drug concentration in the sputum by capillary electrophoresis can help to check the real effectivity of the applied antibiotic. In the case of intubated or mechanically ventilated patients that have chronic bronchopneumonia caused by nosocomial infections, drug monitoring by determination of its concentration in the bronchial secretion might be a method to consider to facilitate appropriate drug selection.

**REFERENCES**


studies and sputum levels of ceftriaxone once daily administration in respiratory tract infection. Jpn. J. Antibiot. 42:921–929.


