Levels of Vancomycin in Cerebrospinal Fluid of Adult Patients Receiving Adjunctive Corticosteroids to Treat Pneumococcal Meningitis: A Prospective Multicenter Observational Study

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Background. Evidence from a recent randomized controlled trial suggests that dexamethasone as adjunct therapy in adult pneumococcal meningitis reduces mortality and neurological sequelae. However, adding dexamethasone has the potential to reduce penetration of vancomycin into the cerebrospinal fluid (CSF). We sought to determine concentrations of vancomycin in serum and CSF of patients with suspected or proven pneumococcal meningitis receiving dexamethasone to assess the penetration of vancomycin into the CSF during steroid therapy.

Methods. In an observational open multicenter study, adult patients admitted to the intensive care unit because of suspected pneumococcal meningitis received recommended treatment for pneumococcal meningitis, comprising intravenous cefotaxime (200 mg per kg of body weight per day), vancomycin (administered as continuous infusion of 60 mg per kg of body weight per day after a loading dose of 15 mg per kg of body weight), and adjunctive therapy with dexamethasone (10 mg every 6 h). Vancomycin levels in CSF were measured on day 2 or day 3 of therapy and were correlated with protein levels in CSF and vancomycin levels in serum (determined at the same time as levels in CSF).

Results. Fourteen patients were included. Thirteen had proven pneumococcal meningitis; 1 patient, initially suspected of having pneumococcal meningitis, was finally determined to have meningitis due to Neisseria meningitidis. Mean levels of vancomycin in serum and CSF were 25.2 and 7.2 mg/L, respectively, and were positively correlated ($r = 0.66; P = .025$). A positive correlation was also found between the ratio of vancomycin in CSF to vancomycin in serum and the level of protein in CSF ($r = 0.66; P = .01$).

Conclusions. Appropriate concentrations of vancomycin in CSF may be obtained even when concomitant steroids are used. Dexamethasone can, therefore, be used without fear of impeding vancomycin penetration into the CSF of patients with pneumococcal meningitis, provided that vancomycin dosage is adequate. This study is registered at http://www.ClinicalTrials.gov/ (registration number NCT00162578).

Streptococcus pneumoniae is the pathogen most commonly isolated from adults with community-acquired meningitis and is responsible for a high rate of deaths and/or neurological sequelae [1–5]. With the dramatic increase in the prevalence of strains that are nonsusceptible to penicillin G, combination therapy with either cefotaxime or ceftriaxone and vancomycin has become the standard empirical antimicrobial therapy. Conceivably, meningitis due to penicillin-nonsusceptible S. pneumoniae might constitute a risk factor for severe prognosis [6], given the limited penetration of many antibiotics (including third-generation cephalosporins) into CSF, even when meningeal inflammation is present [7, 8]. However, penetration of vancomycin into the CSF is far from optimal [7, 9, 10], and the...
vancomycin MIC for *S. pneumoniae* usually ranges between 0.25 and 1 µg/mL [7, 9, 10], which may lead to poorly bactericidal titers in CSF [7, 9]. Moreover, on the basis of the available evidence on the use of adjunctive dexamethasone treatment in adults, especially from a recent controlled study [11], this drug is now recommended for adults with suspected or proven pneumococcal meningitis (10 mg 4 times daily for 4 days).

However, because CSF penetration by hydrophilic antibiotics, such as β-lactams or vancomycin, is strongly influenced by meningeal inflammation [7, 8, 10, 12], concerns have been raised about the possible deleterious effect of high-dose steroids. In fact, the presence of a nonsusceptible strain, combined with insufficient levels of vancomycin in CSF, could delay sterilization of CSF, with negative consequences for clinical outcome. The only large randomized trial that clearly demonstrated an improved prognosis after corticosteroid treatment in adults was conducted among patients who were treated with a β-lactam antibiotic alone, usually amoxicillin [11]. In this study [11], all strains that underwent in vitro susceptibility testing (72% of the total) displayed normal susceptibility to penicillin, but it cannot be excluded that some of the other strains may have been resistant to penicillin. The purpose of this prospective clinical study was to demonstrate that acceptable concentrations of vancomycin may be achieved in the CSF of patients with pneumococcal meningitis treated with dexamethasone, provided high serum levels are obtained as the result of adequate intravenous dosing.

**METHODS**

This prospective study was performed in 4 medical intensive care units of 4 Paris-area hospitals. All consecutive patients >18 years of age who were hospitalized in the participating intensive care units were included, provided that they had proven or suspected pneumococcal meningitis and that a second lumbar puncture was performed on day 2 or day 3 to assess favorable evolution of meningitis. Pneumococcal meningitis was defined as CSF pleocytosis (>10 cells/µL) and one or more of the following criteria: a positive result of culture of CSF or blood; gram-positive diplococci in a direct smear examination of the CSF; or presence of pneumococcal antigens in the CSF detected by a latex agglutination method.

The treatment followed recommendations of the Consensus Conference organized by the French Society of Infectious Diseases [13]. The antibiotic regimen comprised the administration of intravenous cefotaxime (200 mg per kg of body weight per day in 4 divided doses) and intravenous vancomycin (continuous infusion of 60 mg per kg of body weight per day after a loading dose of 15 mg per kg of body weight), pending susceptibility results. Dexamethasone (10 mg every 6 h) was administered intravenously for 4 days, with the first dose given just before or concomitant with the first dose of antimicrobial therapy, according to the methods of de Gans and van de Beek [11]. In addition, patients treated in one of the centers received intravenous rifampin at a dose of 20 mg per kg of body weight per day, as recently suggested [14, 15]. As soon as β-lactam susceptibility results were available, vancomycin (and rifampin) therapy was stopped for patients infected with organisms susceptible to cefotaxime.

On day 2 or day 3 after the start of antimicrobial therapy, serum and CSF samples were obtained simultaneously, and vancomycin concentrations were determined using the fluorescent polarization immunoassay [16]. The susceptibility of *S. pneumoniae* isolates to β-lactam agents and vancomycin was determined for all patients from whom this organism was obtained by culture (12 patients). A 1-µg oxacillin disk was used to identify penicillin-resistant strains. Penicillin G, amoxicillin, and cefotaxime MICs were determined in each hospital laboratory with use of Etest. Vancomycin MICs were determined for 10 patients. Susceptibility categories were assigned according to the 1997 Clinical and Laboratory Standards Institute (then the National Committee for Clinical Laboratory Standards) guidelines for break points [17], as follows: for penicillin G, ≤0.06 mg/L was susceptible, 0.12–1 mg/L was intermediate, and ≥2 mg/L was resistant; for amoxicillin and cefotaxime, ≤0.5 mg/L was susceptible, 1 mg/L was intermediate, and ≥2 mg/L was resistant; for vancomycin, ≤1 mg/L was susceptible. Usual demographic data were collected, including age, weight, simplified acute physiology score II [18], Glasgow coma score, receipt of mechanical ventilation, and outcome.

Data are presented as mean value (± SD). Correlations were calculated with GraphPad Prism 3 statistical software (GraphPad Software). P < .05 was considered to be statistically significant. The study protocol was approved by the Ethical Committee of the French Intensive Care Society. Because the protocol consisted only in the prospective collection of data that were requested for patient care, and because no additional investigational or treatment procedure was requested, formal patient consent was not required, but all procedures and their purposes were explained to the patient or to a proxy in the case of patient incompetence. This study is registered at http://www.ClinicalTrials.gov/ (registration number NCT00162578).

**RESULTS**

Fourteen patients were included in the study. The mean age (± SD) was 52 ± 20 years (range, 19–83 years); 8 patients were male, and 6 patients were female. The mean simplified acute physiology score II (± SD) was 43 ± 20, and the mean Glasgow coma score (± SD) was 7 ± 3. Ten (71%) of 14 patients required mechanical ventilation. All patients had CSF characteristics that
strongly suggested the diagnosis of bacterial meningitis (table 1): pleocytosis was marked, glucose concentrations were very low (mean value, <0.5 g/L), and protein concentrations were very high (>5 g/L in 10 patients, with 4 patients exhibiting a protein concentration of >10 g/L). The maximum protein concentration was 24 g/L, and the lowest protein concentration was 0.81 g/L (in a patient with severe serum hypoproteinaemia).

Thirteen of the 14 patients had confirmed pneumococcal meningitis: in 12 patients, direct examination of CSF yielded results positive for gram-positive cocci, and culture results were positive for S. pneumoniae; in 1 patient, direct examination of CSF yielded positive results for gram-positive cocci, with positive results of S. pneumoniae antigen detection, but culture of CSF did not yield S. pneumoniae. The final patient was initially incorrectly given the diagnosis of pneumococcal meningitis on the basis of a false-positive result of direct smear staining of a CSF sample. Culture (after a follow-up lumbar puncture was performed) eventually yielded a slow growth of Neisseria meningitidis (table 1). Blood culture results were positive for S. pneumoniae in 8 patients.

Susceptibility to β-lactam antibiotics was determined for 12 of 13 pneumococcal isolates available by culture (as mentioned above, CSF samples were sterile in 1 case, but direct examination showed gram-positive cocci, and soluble S. pneumoniae antigens were detected). Seven of the 12 pneumococcal strains were not susceptible to penicillin. One of these 7 isolates was determined to have intermediate susceptibility to amoxicillin and cefotaxime (MIC, 1.5 mg/L). No organism displayed MIC

Table 1. Characteristics of CSF samples obtained from patients with pneumococcal meningitis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>First lumbar puncture</th>
<th>Second lumbar puncture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count, cells/mL</td>
<td>8 ± 27</td>
<td>0.7 ± 0.11</td>
</tr>
<tr>
<td>Protein level, g/L</td>
<td>8.6 ± 7.22</td>
<td>5.4 ± 4.35</td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>0.5 ± 0.77</td>
<td>2.6 ± 1.43</td>
</tr>
<tr>
<td>Gram-positive cocci on direct examination of CSF, no. of patients</td>
<td>13⁺</td>
<td>7</td>
</tr>
<tr>
<td>Positive results of CSF culture for Streptococcus pneumoniae, no. of patients</td>
<td>12⁺</td>
<td>0</td>
</tr>
<tr>
<td>Positive results for soluble S. pneumoniae antigens in CSF, no. of patients</td>
<td>8</td>
<td>ND</td>
</tr>
<tr>
<td>Penicillin-nonsusceptible S. pneumoniae isolates, proportion (%) of isolates</td>
<td>7/12 (58)</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE. Data are mean value (± SD), unless otherwise indicated. ND, not done.

⁺ One sample finally yielded Neisseria meningitidis, and 1 sample was sterile, but direct examination yielded findings positive for gram-positive cocci and for soluble S. pneumoniae antigens.

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Table 2. Vancomycin concentrations in serum and CSF samples, corresponding vancomycin MICs, and outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Vancomycin concentration Serum, mg/L</th>
<th>Vancomycin concentration CSF, mg/L</th>
<th>Vancomycin MIC, mg/L</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35.30</td>
<td>22.30</td>
<td>0.75</td>
<td>Died, irreversible coma</td>
</tr>
<tr>
<td>2</td>
<td>24.0</td>
<td>6.20</td>
<td>0.75</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>39.0</td>
<td>8.70</td>
<td>0.75</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>22.50</td>
<td>4.70</td>
<td>1.00</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>31.90</td>
<td>10.10</td>
<td>0.38</td>
<td>Survived with neurological sequelae</td>
</tr>
<tr>
<td>6</td>
<td>22.20</td>
<td>12.00</td>
<td>0.5</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>28.40</td>
<td>11.70</td>
<td>≤1</td>
<td>Died, septic shock</td>
</tr>
<tr>
<td>8</td>
<td>20.50</td>
<td>3.70</td>
<td>≤1</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>17.62</td>
<td>3.11</td>
<td>NPa</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>27.0</td>
<td>8.30</td>
<td>0.38</td>
<td>Survived</td>
</tr>
<tr>
<td>11</td>
<td>26.4</td>
<td>4.30</td>
<td>NPb</td>
<td>Survived, with neurological sequelae</td>
</tr>
<tr>
<td>12</td>
<td>16.0</td>
<td>3.10</td>
<td>0.38</td>
<td>Survived</td>
</tr>
<tr>
<td>13</td>
<td>32.0</td>
<td>6.40</td>
<td>0.25</td>
<td>Died, irreversible coma</td>
</tr>
<tr>
<td>14</td>
<td>14.2</td>
<td>5.80</td>
<td>0.25</td>
<td>Survived</td>
</tr>
<tr>
<td>All, mean value ± SD</td>
<td>25.5 ± 7.3</td>
<td>7.9 ± 5.1</td>
<td>0.62 ± 0.29</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. NP, not possible.
a CSF eventually yielded Neisseria meningitidis.
b CSF was sterile but direct examination yielded findings positive for gram-positive cocci and CSF was positive for soluble Streptococcus pneumoniae antigens.
\[ r = 0.68; P = .01 \]

**Figure 1.** Correlation between levels of vancomycin in serum and CSF in patients with meningitis. The bold arrow indicates the patient who was eventually determined to have meningitis due to *Neisseria meningitidis.*

\[ \geq 2 \text{ mg/L}. \text{ All strains were susceptible to vancomycin. In the 10 patients for whom it was determined, the vancomycin MIC for } S. \text{ pneumoniae was } 0.125–1 \text{ mg/L (table 2).} \]

All patients received the protocol-recommended antibiotic regimen, consisting of cefotaxime and vancomycin. Six patients received intravenous rifampin in addition (see Methods). In 1 patient, who had severe chronic renal insufficiency, dosages of cefotaxime and vancomycin were adapted according to renal function. A second lumbar puncture was performed on day 2 for 4 patients and on day 3 for 10 patients. Characteristics of CSF samples obtained during the second lumbar puncture are shown in table 1. There was a marked improvement in all parameters, with pronounced decreases in protein concentrations and increases in glucose levels. Bacterial culture results were negative for all patients. The antibiotic regimens were adapted according to antibacterial susceptibility results (i.e., discontinuation of vancomycin—and of rifampin when added—except for the patient with isolates with intermediate susceptibility to cefotaxime). Three patients died (2 of irreversible coma and 1 of concomitant pneumococcal septic shock). Two other patients were discharged from the intensive care unit with severe neurological sequelae, and the 9 remaining patients resumed normal neurological status and were discharged from the hospital.

The mean concentration of vancomycin in serum samples was 25.2 mg/L (range, 14.2–39.0 mg/L). The mean concomitant concentration of vancomycin in CSF samples was 7.9 mg/L (range, 3.1–22.3 mg/L). Table 2 shows individual and mean values for vancomycin concentrations. A significant correlation was found between vancomycin concentrations in serum and CSF samples (\( r = .68; P = .01 \)) (figure 1). This correlation remained unchanged when the patient, who was finally determined to have meningococcal meningitis, was excluded from the study. There was also a significant correlation between the concentration of protein and the ratio of vancomycin concentration in CSF to the same values for serum (figure 2). The outlier, with a very low protein concentration in CSF samples, corresponded to a severely malnourished patient with a very low protein concentration in plasma samples. Mean blood urea and creatinine concentrations were 6.2 mmol/L and 84.4 \( \mu \text{mol/L} \), respectively (excluding 1 patient undergoing chronic renal replacement).

**DISCUSSION**

To the best of our knowledge, this is the first clinical study evaluating the role of high-dose systemic vancomycin administration in the achievement of adequate CSF levels of this antibiotic in patients receiving adjunctive dexamethasone treatment for bacterial meningitis. Acceptable levels of vancomycin were obtained in CSF samples obtained from all of our patients: none had <3.1 mg/L, and the mean value was 7.9 mg/L (or 30% of the simultaneously determined concentration in serum samples). All pneumococcal isolates in our study were susceptible to vancomycin, and MICs were in the range of published data [9, 10]. As a result, the concentration of vancomycin in CSF was at least 10-fold the MIC in 8 patients, 8-fold the MIC in 2 patients, and 4-fold the MIC in 1 patient (table 2). These high doses may be needed to achieve acceptable bactericidal titers in CSF.

More importantly, penetration of vancomycin into CSF was found to be linearly correlated with the concentration of vancomycin in serum. This correlation was not altered when the patient who was finally given the diagnosis of meningococcal meningitis was excluded. We chose to retain this patient in the analysis, because he received exactly the same initial treatment.
Dosages (15 mg per kg of body weight 3 times daily) had vancomycin levels in CSF of 4–9.4 mg/L. A continuous-administration schedule with a loading dose was used because we previously demonstrated that targeted serum levels were obtained more rapidly with continuous than with intermittent administration of vancomycin [20]. There is, however, no reason to think that results would be markedly different if intermittent administration was used, as recommended in the United States.

As expected, we found that vancomycin penetration into the CSF was correlated with protein levels in CSF, which is a marker of blood-brain barrier permeability caused by meningeal inflammation. The anti-inflammatory effects of corticosteroids on vancomycin penetration into the CSF are debated. Dexmethasone reduced the penetration of vancomycin into CSF by 20%–30% during experimental studies of pneumococcal meningitis [21–24]. Data in humans are conflicting: children receiving adjunctive steroids had acceptable levels of vancomycin in CSF during pneumococcal meningitis [25], whereas vancomycin levels were low or even undetectable in CSF samples obtained from adults with pneumococcal meningitis [9]. Our results suggest that the possible impairment of vancomycin penetration into CSF could be overcome by increasing the dosage of vancomycin, as previously suggested [23]. Moreover, serum and CSF concentrations of vancomycin were very close to those previously reported for patients receiving similar high dosages for the treatment of postneurosurgical meningitis and who were not treated with dexamethasone [26]. This observation prompted us to plot vancomycin concentrations in serum and CSF measured in various conditions (experimental or clinical and with or without corticosteroids) on the same graph. We identified 6 studies [9, 21, 23, 25–27] that reported both serum and CSF levels of vancomycin. Thus, including our own results, 12 sets of paired serum and CSF vancomycin concentrations were plotted (figure 3). We were surprised to observe a highly significant linear relationship, with a very high slope (0.32) that was not significantly different from the slope observed in this study (0.42).

Figure 3. Mean levels of vancomycin in CSF, compared with mean levels of vancomycin in serum, in experimental and clinical studies of pneumococcal meningitis. Only those studies that explicitly reported concomitant serum and CSF levels of vancomycin were included. Seven studies, including the present study, were identified. Experimental studies sometimes compared conditions with and without dexamethasone, thus providing a total of 12 data points. There was a strong positive correlation between serum and CSF levels of vancomycin. Open circles, clinical studies that used dexamethasone [9], including our study (arrow); open squares, experimental studies with dexamethasone [21, 23, 27]; solid circles, clinical studies in which treatment did not include use of dexamethasone [25, 26]; solid squares, experimental studies without dexamethasone [23, 27].
rule out in critically ill patients, this high-dosage regimen seemed to be well tolerated by our patients: no skin rash or unexplained hemodynamic instability were observed, and there was no alteration of renal function that could be specifically related to the treatment regimen.

Our study was a pragmatic one that consisted of the evaluation of recent recommendations for treatment of these patients [15]. Indeed, it may be very difficult, if not impossible, to conduct a randomized, controlled study on this subject [28].

Acknowledgments

This article is dedicated to the memory of Dr. Arnaud de Lassence.

Potential conflicts of interest. All authors: no conflicts.

References