Treatment of staphylococcal ventriculitis associated with external cerebrospinal fluid drains: a prospective randomized trial of intravenous compared with intraventricular vancomycin therapy

Bettina Pfausler, M.D., Heinrich Spiess, M.D., Ronny Beer, M.D., Andreas Kampff, M.D., Klaus Engelhardt, M.D., Maria Schober, M.D., and Erich Schmutzhard, Univ. Prof.

Department of Neurology and the Central Laboratories, University Hospital, Innsbruck, Austria

Object. Staphylococcal ventriculitis may be a complication in temporary external ventricular drains (EVDs). The limited penetration of vancomycin into the cerebrospinal fluid (CSF) is well known; the pharmacodynamics and efficacy of systemically compared with intraventricularly administered vancomycin is examined in this prospective study.

Methods. Ten patients in whom EVDs were implanted to treat intracranial hemorrhage and who were suffering from drain-associated ventriculitis were randomized into two treatment groups. Five of these patients (median age 47 years) were treated with 2 g/day vancomycin administered intravenously (four infusions/day; Group 1), and the other five (median age 49 years) received 10 mg vancomycin intraventricularly once daily (Group 2). Vancomycin levels were measured in serum and CSF six times a day. The maximum vancomycin level in CSF was 1.73 ± 0.4 µg/ml in Group 1 and 565.58 ± 168.71 µg/ml 1 hour after vancomycin application in Group 2 (mean ± standard deviation). Vancomycin levels above the recommended trough level of 5 µg/ml in CSF were never reached in Group 1, whereas in Group 2 they were below the trough level (3.74 ± 0.66 µg/ml) only at 21 hours after intraventricular vancomycin application. The vancomycin level in the serum was constant within therapeutic levels in Group 1, whereas in Group 2 in most instances vancomycin was almost below a measurable concentration. In both groups bacteriologically and laboratory-confirmed CSF clearance could be obtained.

Conclusions. Intraventricular vancomycin application is a safe and efficacious treatment modality in drain-associated ventriculitis, with much higher vancomycin levels being achieved in the ventricular CSF than by intravenous administration.

Key Words • ventriculitis • intraventricular vancomycin

Intracranial and, in particular, intraventricular hemorrhages frequently lead to an occlusive hydrocephalus necessitating the implantation of an EVD. These EVDs, which are used as temporary tools to control raised intracranial pressure caused by CSF obstruction, are associated with a progressive infection resulting in ventriculitis in up to 39% of patients. The organisms involved are predominantly Gram-positive bacteria, and coagulase-negative staphylococci are most common. In noninflamed meninges, penetration of various antibiotics, for example vancomycin, into the CSF is poor; in acute meningitis, however, it may reach significantly higher levels in CSF, with CSF/serum ratios of up to 48%. Because vancomycin has a slow bactericidal activity with a low minimum inhibitory concentration and a time-dependent activity when administered by intermittent intravenous administration, continuous infusion of vancomycin has been proposed to achieve a constant bactericidal level in blood, with consequently better CSF penetration. In staphylococcal ventriculitis, the inflammation of the meninges and ventricular ependyma is usually mild to moderate, thus allowing a potentially insufficient level of bactericidal activity within the ventricular compartment, even by continuous intravenous infusion. In several case reports and smaller case series the successful treatment of an EVD-associated ventriculitis with intraventricular administration of vancomycin has been described. Nevertheless, the dosage for intraventricular application has been chosen empirically, and the pharmacokinetic findings within the CSF, in particular over a prolonged period of treatment, have not been studied in detail. Recently, we reported on vancomycin levels in the CSF of three patients with EVD-associated ventriculitis; in all patients the intraventricular vancomycin was administered as a single daily dose of 10 mg. Only limited data exist on the pharmacokinetics of vancomycin, however, either for intraventricular or intravenous administration. Therefore, we conducted a prospective randomized study in which our aim was to compare the pharmacokinetics of vancomycin in the CSF and serum after intraventricular or intravenous vancomycin administration. The study was approved by our institution’s internal review board.
Vancomycin therapy in staphylococcal ventriculitis

Clinical Material and Methods

Patient Population

Patients older than 18 years of age who needed an EVD for intraventricular hemorrhage and in whom a drain-associated ventriculitis developed subsequently were eligible. The diagnosis of ventriculitis was confirmed by local (CSF) signs of inflammation, including polymorphonuclear pleocytosis and a reduced CSF/serum glucose ratio; by the culture of staphylococci (coagulase-negative Staphylococcus sp. in eight cases and S. aureus in two) from the ventricular CSF; and by systemic signs of inflammation (increased C-reactive protein, polymorphonuclear pleocytosis, and fever). Patients who had not been allowed to receive other antibiotic treatment up to this point were randomized into two groups as described later. The primary end point of the study was the evaluation of the vancomycin pharmacokinetics in both CSF and serum after intraventricular or intravenous administration; the secondary end point was clinical cure and eradication of the staphylococcal infection.

After approval of the study protocol by the institutional review board, five patients fulfilling the inclusion criteria were randomized into each of the two groups (patients were eligible who had definite EVD-associated staphylococcal ventriculitis, were older than 18 years of age, and were receiving no antibiotic treatment). Of 102 consecutive patients with EVDs seen over a period of 30 months, ventriculitis developed in 19, nine of whom were not eligible because they did not fulfill the randomization criteria. Staphylococcal ventriculitis had developed in these 19 patients after a mean of 9 days. None of our patients with EVDs had received prophylactic antibiotic agents. As is routine in such cases, in all 10 patients the ventriculostomy catheter was replaced immediately after the diagnosis of ventriculitis and before the institution of therapy.

Treatment Groups

Patients in Group 1 received 500 mg vancomycin intravenously four times a day (that is, the regular regimen) through a central venous line. Close monitoring of renal function was part of the therapeutic regimen, which allowed the quickest possible adaptation of intravenous dosage if necessary. In Group 2 vancomycin was administered intra-venticularly in a dosage of 10 mg per day, at a concentration of 10 mg/ml. Vancomycin was instilled through the EVD as close as possible to the burr hole. Immediately after instillation of the vancomycin the drain was flushed with 2 ml of NaCl and clamped for 1 hour, thus ensuring the best possible protection against vancomycin contamination of the CSF sampled from the same drain afterward.

Vancomycin levels were measured in both groups in serum and CSF 1 hour after the first daily intravenous or intraventricular administration and then every 4 hours thereafter (that is, at 5, 9, 13, 17, and 21 hours). Measurements of the drug levels were continued in this mode throughout the entire period of vancomycin therapy. The CSF was examined daily for cell count, protein, and glucose levels, and CSF and blood cultures were obtained once a day. White blood cell counts and C-reactive protein were measured twice daily, and body temperature was taken every 2 hours. Both therapy modalities were continued until an apparent clinical, microbiological, and laboratory/chemical cure (based on CSF and serum findings) was achieved. Vancomycin levels were measured using a fluorescence polarization immunoassay (TDx/TDx, FLx Vancomycin; Abbott Laboratories, Vienna, Austria) after centrifugation (2.123 G for 7 minutes at 14 ± 5°C). A size of five patients per group was calculated to be sufficient to reach statistical significance for both treatment groups, when taking into account the difference in CSF concentrations for the two application modalities of, on average, up to 20-fold. Results are presented as the means ± SD. Statistical analysis was done with the Mann-Whitney U-test for unpaired data by using a statistical software program (GraphPad Software, Inc., San Diego, CA). A probability value of less than 0.05 was considered significant.

Results

In all 10 patients the EVD was necessary because occlusive hydrocephalus after spontaneous subarachnoid hemorrhage and spreading of the blood into the ventricular system. All patients were monitored in the neurointensive care unit of the Department of Neurology; a central venous catheter and an arterial line were placed in all of them. The median age in Group 1 (intravenous vancomycin administration) was 47 years (range 27–73 years; two men and three women), and in Group 2 (intraventricular vancomycin administration) it was 49 years (range 26–73 years; one man and four women)

Group 1

In Group 1 the mean serum Vancomycin levels were 25.94 ± 1.44 μg/ml after 1 hour (Table 1). After 5 hours, that is, 1 hour before the second daily dose of 500 mg vancomycin, the mean level was 13.29 ± 2.22 μg/ml. This represented the lowest serum level in the intravenous vancomycin group. The vancomycin levels measured in the CSF never rose above 5 μg/ml, except in one patient on Day 4 and 7. Throughout the entire treatment period the vancomycin levels in the serum were well within the therapeutic range, showing a tendency to accumulate (Table 2).

Group 2

In Group 2, vancomycin was administered intraventricularly once daily. The highest vancomycin levels in the CSF were seen at 1 hour after application and clamping of the drainage system, with values of 565.58 ± 168.71 μg/ml
and the lowest were seen 21 hours after intraventricular vancomycin administration, with a mean level in the CSF of 3.74 ± 0.66 μg/ml (Table 3). In contrast, the serum vancomycin levels in this group were less than 5 μg/ml in most cases, in many instances below measurable concentrations; only in a single instance were serum levels of 8.8 μg/ml reached. The maximum vancomycin levels in the CSF were far above the therapeutic range, whereas in the first 5 days the minimum concentrations (usually obtained at the 21-hour time point) were below the trough level, showing a slight tendency to accumulate (Table 4).

In both groups, bacteriologically and laboratory/chemically confirmed clearance of the CSF were obtained within 3 to 4 days of vancomycin therapy; the pre- and posttreatment CSF data are shown in Table 5.

No clinically or bacteriologically confirmed relapses were observed. Results of cultures of CSF were negative on days 2 to 3 in Group 2 and on days 3 to 4 in Group 1. Thus, the antibiotic treatment was continued for 3 to 4 days after bacteriologically confirmed clearance of the CSF. No toxicity was observed, and in particular no CSF toxicity in either of the two groups. The patients received neurological, electroencephalographic, and neuroimaging follow up within 6 months of discharge, with no findings that were compatible with a toxic reaction within the central nervous system.

### Discussion

Vancomycin is known to have excellent efficacy against methicillin-resistant staphylococci; this efficacy, however, is hampered by poor CSF penetration. The capability of penetrating the meninges depends mainly on the intensity of the inflammatory reaction of the meninges and the ventricular ependyma. In nosocomial EVD-associated staphylococcal ventriculitis the ventricular ependyma normally shows only a mild to moderate inflammatory reaction, which may be responsible for insufficient vancomycin penetration of the BBB. Several authors have reported on the successful treatment of nosocomial staphylococcal ventriculitis by means of intraventricular administration of low doses of vancomycin. The exact dose for intraventricular vancomycin application, however, still remains controversial, with 10 and 20 mg/day being most frequently used. Bayston and colleagues recommend a minimal trough level of 5 μg/ml in the CSF for staphylococcal ventriculitis to achieve a microbiologically confirmed cure. Despite high vancomycin levels in the serum of all our patients receiving the drug intravenously, this minimal trough level could only be achieved in one case. The highest mean CSF concentrations in our study were 1.73 ± 0.4 μg/ml measured 3 hours after the second daily intravenous vancomycin application, and in only one case did the vancomycin level reach 7.8 μg/ml, which occurred 1 hour after the first dose of 500 mg vancomycin on Day 6. The serum level of vancomycin measured in parallel at this time point was 37 μg/ml. Importantly, however, despite these extremely low and insufficient CSF levels, which were almost always far below the suggested minimal trough level of 5 μg/ml for the drug, all patients showed clinically and laboratory/chemically confirmed cure and bacteriologically verified clearance of the CSF.

Interestingly, several authors propose an even higher daily dosage of vancomycin (up to 60 mg/kg/body weight four times daily) for the treatment of catheter-related ventriculitis. Nevertheless, vancomycin levels in the CSF and serum have not been measured in patients receiving these vancomycin dosages. The proposed curative CSF

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**Table 2**

Highest and lowest mean vancomycin levels in CSF and serum in five patients after intravenous infusion

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>No. of Patients</th>
<th>Highest (mean ± SD)</th>
<th>Lowest (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin level in CSF (μg/ml)</td>
<td>1</td>
<td>5</td>
<td>0.96 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5</td>
<td>1.72 ± 0.34</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>1.58 ± 0.62</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>5</td>
<td>3.85 ± 2.31</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>2.83 ± 1.29</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>5</td>
<td>2.85 ± 1.70</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4</td>
<td>5.15 ± 3.65</td>
</tr>
</tbody>
</table>

**Table 3**

Mean vancomycin levels in CSF and serum after intraventricular administration

<table>
<thead>
<tr>
<th>Sampling Time (hrs)</th>
<th>No. of Samples</th>
<th>CSF (μg/ml)</th>
<th>Serum (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>565.58 ± 168.71</td>
<td>3.64 ± 1.48</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>59.00 ± 34.08</td>
<td>0.44 ± 0.39</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>13.46 ± 1.60</td>
<td>0.15 ± 0.09</td>
</tr>
<tr>
<td>13</td>
<td>33</td>
<td>8.34 ± 1.17</td>
<td>0.07 ± 0.07</td>
</tr>
<tr>
<td>17</td>
<td>33</td>
<td>5.61 ± 0.84</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>21</td>
<td>33</td>
<td>3.74 ± 0.66</td>
<td>0.12 ± 0.08</td>
</tr>
</tbody>
</table>

* Single dose of 10 mg per day at 0 hours.

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trough levels may need to be reconsidered in case of EVD-associated staphylococcal ventriculitis. In the intraventricular treatment group, in which the vancomycin dosage was 10 mg once daily, the drug could be measured in the CSF at all time points, except in one case during the first 2 treatment days. Only at 17 and 21 hours after intraventricular vancomycin administration were trough levels of less than 5 μg/ml measured in eight of 33 and 21 of 33 instances, respectively. In contrast with the high vancomycin levels 1 hour after intraventricular vancomycin administration, only extremely low levels of vancomycin could be measured at the same time in the serum. Only at 1 hour after intraventricular administration was the mean serum vancomycin level measurable (3.64 ± 1.48 μg/ml). The question of whether these low serum vancomycin levels may contribute to the potential risk that drug resistance will develop in staphylococci or other bacterial strains should be further investigated.

Albanese et al., measured vancomycin levels in the CSF through an EVD when the drug was administered by continuous intravenous infusion in seven patients who had a vancomycin-sensitive bacterial meningitis and in six more patients who had a noninfectious concomitant neurological disease accompanied by intracranial hypertension and who were treated for nonneurological infections. In the patients with meningitis the minimal mean CSF vancomycin levels were 6.2 ± 4.08 mg/ml, ranging from 1.6 to 11.1 mg/ml. In contrast to our patients, these individuals obviously had a community-acquired meningitis, a fact that clearly distinguishes this group of patients from ours, in whom the main infectious process was localized within the lateral ventricles, the ventricular CSF, and the ventricular ependyma. This fact needs to be considered because the level and extension of inflammatory changes is clearly correlated with the capability of vancomycin to penetrate the BBB. A community-acquired meningitis involves all the meninges, that is, a large area of the BBB, and usually leads to a much more prominent breakdown of this barrier. For this reason it seems noteworthy that after intraventricular administration the vancomycin levels in CSF were still above 5 μg/ml, even 17 hours after the single intraventricular daily dose.

The possible toxicity of vancomycin directly administered into the CSF is controversial. Despite the initially extremely high vancomycin levels in the CSF, no toxic complications or side effects, either local or within the entire central nervous system, were observed, even in a 6-month follow up including neurological, neuroimaging, and electrophysiological examination. No signs and symptoms attributable to a potential toxic effect were found. All neurological signs and symptoms at the 6-month follow up were attributable to the primary neurological disease.

Conclusions

Our study demonstrates that with intraventricular administration of 10 mg vancomycin, an EVD-associated staphylococcal ventriculitis can be cured in less than 7 days, with both clinical and microbiological confirmation. With intravenous administration of 2000 mg vancomycin per day, CSF levels above the preferred trough value of 5 μg/ml were not achieved. All five patients, however, had a clinically and microbiologically confirmed cure within similar time periods. Because in patients with an EVD-associated staphylococcal ventriculitis in most cases a single bacterial strain is the causative agent (in most instances coagulase-negative staphylococci), obviously lower levels may also be sufficient to eradicate this type of bacterial pathogen. Nevertheless, the extremely low and only intermittently measurable serum levels of vancomycin after intraventricular administration of 10 mg should give rise to caution. The possible risk of further development of vancomycin-resistant enterococci, clostridia, or other bacteria needs to be assessed, monitored, and observed very closely.

Despite these caveats, our study shows that in patients in whom intravenous administration of vancomycin is relatively contraindicated (for example, those with renal insufficiency), the intraventricular administration of this drug in patients with EVD-associated staphylococcal ventriculitis may be recommended as an equally efficacious treatment modality that achieves much higher levels of vancomycin in the ventricular CSF than with intravenous administration. Also, vancomycin elimination might be hampered in patients in intensive care with multiorgan dysfunction, increasing the risk of side effects. Matzke, et al., pointed to hepatic conjugation as an important means of vancomycin elimination. Finally, the economic aspect of using a daily dosage of 10 mg compared with 2000 mg for a period of up to 7 days in a time of extreme economic restriction bears mentioning.

References


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Address reprint requests to: Bettina Pfausler, M.D., Department of Neurology, University Hospital Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria. email: b.pfausler@uibk.ac.at.