Treatment Optimization by Monitoring Vancomycin Concentration in the Serum and Cerebrospinal Fluid in a Child with Cystoperitoneal Shunt-related Infection Caused by Methicillin-resistant Staphylococcus aureus: A case report

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Case Report

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Abstract

Background

Cerebral ventricular shunt infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), especially strains with elevated minimal inhibitory concentration (MIC) values, have a poor prognosis. Monitoring serum vancomycin (VCM) levels with therapeutic drug monitoring and maintaining high VCM concentrations in the cerebrospinal fluid (CSF) are critical to treatment success. However, there have been a few reports about CSF penetration and the pharmacokinetics of VCM in children.

Case presentation

Here, we report a pediatric case with cystoperitoneal shunt-related meningitis caused by MRSA with an MIC of 2 µg/mL. The adequate VCM concentration was maintained by monitoring the VCM concentration in the CSF via the external ventricular drain, and frequent blood taking was avoided. VCM showed a good CSF penetration in our patient, and she was discharged without complications.

Conclusions

Therapeutic drug monitoring of VCM concentration in the CSF may result in successful treatment even if MRSA shows a higher MIC. Therapeutic drug monitoring of VCM concentration in the CSF may also reduce the frequency of blood collection and side effects.

Background

The reported post-neurosurgical central nervous system (CNS) infection incidence varies from less than 1% to as high as 8.6%. [1, 2, 3] The ventriculoperitoneal (VP) shunts are used more often, having an infection rate of 11.7% (range 4.1–20.5%) and a high mortality rate between 15% and 23%. [1, 4] Cerebral ventricular shunt infection can be improved with appropriate treatment. However, the emergence of antimicrobial-resistant pathogens raised worldwide concerns, leading to a decline in treatment choices and adversely affecting outcomes. [5]

Vancomycin (VCM) has a bactericidal and time-dependent activity with limited penetration in the cerebrospinal fluid (CSF) because of its hydrophilicity and large molecular size. [6] Therefore, high serum levels of antibiotic concentration are needed to achieve an appropriate CSF concentration. However, the penetration of VCM is not universally low, but variable and unpredictable, depending on patient factors. [7, 8]

The recent Infectious Disease Society of America guidelines recommend VCM for treating CNS infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and that its trough levels should be kept at 15–20 µg/mL. They also propose a second-line drug such as linezolid if the strain’s minimal inhibitory
concentration (MIC) value is 2 µg/mL, and if the patient does not show clinical improvement with treatment with VCM. [1]

According to the patient factors, there have been a few reports about CSF penetration and pharmacokinetics of VCM in children. Central nervous system (CNS) inflammation facilitates antibiotic diffusion into the CSF because of the opening of the tight junctions of the blood-brain-barrier cells during the acute phase of CNS infection. [7, 8] However, intense meningeal inflammation is absent in cerebral ventricular shunt infection. Thus, cerebral ventricular shunt infection may be associated with low CSF drug levels. [7, 9]

Here, we report a pediatric case with cystoperitoneal shunt-related infection caused by MRSA with an elevated MIC value of 2 µg/mL. We successfully treated with VCM by therapeutic drug monitoring (TDM) of VCM concentration in the blood and CSF. Additionally, monitoring the VCM concentration in the CSF may help make decisions about changing second-line drugs and reducing the frequency of side effects by avoiding unnecessary high levels of serum VCM concentration.

Case Presentation

A 2-year-old girl was admitted to our hospital for endoscope-assisted fenestration of the intracranial cysts and shunt valve replacement surgery against cysto-peritoneal (CP) shunt dysfunction. The patient was delivered normally at the gestational age of 37 weeks and 2 days. The pregnancy was uneventful. Her birth weight was 3,214 g, her height was 49.0 cm, and her head circumference was 43.1 cm. Her past medical history included congenital multiple intracranial cysts. Pathological examination of the tissue sample at 8 days of life revealed cerebral malformation. A CP shunt was placed 1 month after birth.

Four days after the operation (day 1), she developed a fever and irritability. On physical examination, she was febrile with a temperature of 39.5°C, tachycardic, tachypneic, had a Glasgow Coma Scale of E3V5M6, and showed nuchal rigidity. However, she had no neurological deficits. The patient’s laboratory data were white blood cell count, 13.7 × 10^9 /L and C-reactive protein, 19.4 mg/dL. CSF examination revealed a high cell count of 236 /µL (54.7% mononuclear cells, 45.3% polymorphonuclear cells), a slightly high total protein concentration (10.6 g/L), and a slightly low glucose concentration (2.6 mmol/L). Gram staining of the CSF detected gram-positive cluster microorganisms. We initiated intravenous VCM and cefepime. MRSA was isolated from the CSF on day 2; these isolates were susceptible to VCM when the MIC was elevated to 2 µg/mL (Table 1), and cefepime was discontinued. The time to positivity for the CSF culture was 5 h. The CP shunt was removed, and an external ventricular drain (EVD) was placed on the same day. A shunt culture was also positive for MRSA.

The VCM levels in the serum and CSF obtained from the EVD tube were measured during treatment (Table 2). The dosage of VCM was adjusted to achieve both a CSF trough level of at least 2.0 mg/L and a serum trough level of less than 20 mg/L, resulting between 70 mg/kg/d to 100 mg/kg/d. The median VCM serum trough level was 13.7 mg/L (interquartile range [IQR]: 10.7 to 15.2 mg/L), and the serum peak
level was 20.1 mg/L on day 8. The median CSF trough level was 5.3 mg/L (IQR: 4.1 to 5.9 mg/L), and the median CSF/serum concentration ratio was 0.29 mg/L (interquartile range: 0.28 to 0.42 mg/L). Her serum creatinine levels showed a normal range during treatment with VCM.

On day 3, her symptoms improved. Lumber punctures were performed on day 6, with no MRSA growth shown. On day 16, brain magnetic resonance imaging was performed, and no findings of abscess formation showed. Antibiotic treatment was ended on day 29, and the CP shunt was placed on day 34. The patient was discharged without any complications on day 42.

**Discussion And Conclusions**

In this study, we successfully treated cystoperitoneal shunt-related infection caused by MRSA with an elevated MIC of 2 µg/mL by monitoring both CSF and serum concentration levels of VCM. The penetration rate of VCM from the blood to CSF was shown to be high enough.

The estimates using in vitro data showed that even if the dosage of VCM increased, the target concentration for CNS infection caused by MRSA with an elevated MIC of 2 µg/mL could not be achieved by pharmacokinetics/pharmacodynamics theory. [6] However, some reports have previously shown controversial results. The Infectious Disease Society of America guideline states that VCM can be continued if the patients improve clinically because one point of MIC difference can occur by laboratory error and the MIC result varies based on the method used. [1, 10–13]

Data on CSF penetration and pharmacokinetics of VCM in children is very rare. While the penetration rate of VCM was variable (6 to 81%) among adult patients with acute bacterial meningitis, the penetration rate was reported to be a narrower range (0 to 68%) in children. [7, 8, 15] This variability could be caused by several factors. Some reports described a higher penetration rate from the blood to CSF, delayed removal by a decrease of the CSF bulk flow, and inhibited activity by efflux pump of antibiotics during the acute phase of bacterial meningitis. [7, 8, 15] Otherwise, intense inflammation was not regularly present in cerebral ventricular shunt-related infection. However, there have been some reports that the patients with cerebral ventricular shunt- or EVD-related infection showed relatively higher levels of antibiotics concentration in the CSF than those without these devices because of the disruption of the blood-CSF barrier. [16–19]

In our patient, although the strain isolated from the CSF showed an elevated MIC of 2 µg/mL, successful treatment with VCM was achieved by monitoring the concentration in both the serum and CSF. The penetration rate in our patient was similar to previous studies in children. The trough VCM concentration in the CSF showed that our patient achieved 100% time above the MIC in the CSF during treatment, even after improvement in the symptoms and CSF findings.

High serum VCM concentration can cause complications such as nephrotoxicity, ototoxicity, and vasculitis. [5] Thus, repeated blood sample collections for serum TDM are needed. However, this is difficult in pediatric patients for technical reasons. In our patient, the CSF concentration was high enough.
Therefore, we could avoid unnecessary dose increases. Tolerance was excellent, and no clinically significant adverse events were observed.

A limitation of this report is the use of trough concentration for assessment. As the best pharmacokinetics and pharmacodynamics theory, the area under the curve divided by the MIC is a better parameter than the trough. [7, 20] However, the area under the curve divided by the MIC has not yet been established as a measure of VCM efficacy in pediatric patients. Moreover, multiple blood samplings are required, which may be a burden for both the patient and the medical staff. Therefore, this case shows that using trough concentration as a proxy for efficacy may be a more practical indicator. Therefore, further studies with a large number of cases are needed.

In conclusion, when the CSF can be collected easily through a ventricular shunt or EVD, monitoring the VCM concentration in the CSF combined with its serum concentration as indicators, may be useful in patients with ventriculitis. Moreover, monitoring the VCM concentration in the CSF may help make decisions about changing second-line drugs and avoid unnecessary dosage increases.

List Of Abbreviations

central nervous system, CNS; cerebrospinal fluid, CSF; cysto-peritoneal, CP; external ventricular drain, EVD; magnetic resonance imaging, MRSA; minimal inhibitory concentration, MIC; therapeutic drug monitoring, TDM; Vancomycin, VCM; ventriculoperitoneal shunt, VP shunt

Declarations

Ethics approval and consent to participate:

The Institutional Review Board of the Kobe Children's Hospital (no. R4-143) approved this study protocol.

Consent for publication:

Informed consent was obtained from parents.

Availability of data and materials:

The datasets generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

None.
Authors’ Contributions

Dr. SM conceptualized the study, collected data, analyzed and interpreted data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Drs. JK, HK, and MK collected data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Acknowledgements

Not applicable.

References


Tables

Table 1. Antimicrobial susceptibility profile of Staphylococcus aureus isolated from the blood and cerebrospinal fluid of the patient
<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (mcg/ml)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>&gt; 8</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&gt; 8</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Imipenem</td>
<td>4</td>
<td>R</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;= 2</td>
<td>R</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt; 4</td>
<td>R</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>&gt; 4</td>
<td>R</td>
</tr>
<tr>
<td>Sulfamethoxazole / Trimethoprim</td>
<td>&lt;= 1</td>
<td>R</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>&lt;= 2</td>
<td>S</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>0.5</td>
<td>S</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>&gt; 2</td>
<td>R</td>
</tr>
<tr>
<td>Minocycline</td>
<td>&gt; 8</td>
<td>R</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>&lt;= 0.5</td>
<td>S</td>
</tr>
</tbody>
</table>

S = Susceptible, R = Resistant.

**Table 2.** Vancomycin dose and concentration in the serum and cerebrospinal fluid collected from the extraventricular drain during treatment.

<table>
<thead>
<tr>
<th></th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 12</th>
<th>Day 14</th>
<th>Day 17</th>
<th>Day 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (mg/L)</td>
<td>7.9</td>
<td>8.4</td>
<td>10.7</td>
<td>20.1</td>
<td>13.7</td>
<td>11.3</td>
<td>15.2</td>
<td>14.6</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>CSF (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.9</td>
<td>5.9</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Serum / CSF</td>
<td>0.43</td>
<td>0.29</td>
<td>0.28</td>
<td>0.28</td>
<td>0.27</td>
<td>0.42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose (mg/kg/d)</td>
<td>80</td>
<td>90</td>
<td>100</td>
<td>75</td>
<td>75</td>
<td>72</td>
<td>72</td>
<td>72</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Cre (mg/dL)</td>
<td>0.19</td>
<td>0.20</td>
<td>0.23</td>
<td>0.28</td>
<td>0.25</td>
<td>0.26</td>
<td>0.26</td>
<td>0.26</td>
<td>0.28</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: CSF, cerebrospinal fluid; Cre, creatinine