



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 and literature review

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Abstract

Background Cerebral ventricular shunt infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), especially strains with elevated minimum 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 the CSF penetration and the pharmacokinetics of VCM in children.

Case presentation Here, we report the case of a pediatric patient with cysto-peritoneal 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.

Discussion 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 side effects.

Keywords Therapeutic drug monitoring · Methicillin-resistant *Staphylococcus aureus* · Cysto-peritoneal shunt

Background

Post-neurosurgical central nervous system (CNS) infections can occur in 1%–8.6% of cases and can be treated, but antimicrobial-resistant pathogens are a growing concern and limit treatment options [1–4]. Therapeutic drug monitoring (TDM) is recommended to ensure appropriate antimicrobial therapy for antimicrobial agents with a narrow range of efficacy and toxicity. The drug concentration is measured, and the optimal dosage and administration method are

established based on pharmacokinetics/pharmacodynamics theory [5].

Vancomycin (VCM) has a time-dependent activity with limited penetration in the cerebrospinal fluid (CSF) because of its hydrophilicity and large molecular size [5]. Therefore, a high serum concentration is needed to achieve an appropriate CSF concentration. However, the penetration of VCM is variable and unpredictable, depending on patient factors [6, 7].

The recent guidelines recommend VCM for treating CNS infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). However, these recommendations are primarily based on data from adult populations. They also propose a second-line drug if the strain's minimum inhibitory concentration (MIC) value is 2 µg/mL [1].

Here, we report the case of a pediatric patient with cysto-peritoneal shunt-related infection caused by MRSA with MIC value of 2 µg/mL. We successfully treated with VCM by monitoring both CSF and serum concentration levels of VCM.

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Table 1 Antimicrobial susceptibility profile of *Staphylococcus aureus* isolated from the blood and cerebrospinal fluid of the patient

Antimicrobial	MIC (mcg/mL)	Interpretation
Penicillin	> 8	R
Ampicillin	> 8	R
Cefazolin	16	R
Imipenem	4	R
Gentamicin	< = 2	R
Erythromycin	> 4	R
Levofloxacin	> 4	R
Sulfamethoxazole/Trimethoprim	< = 1	R
Vancomycin	2	S
Teicoplanin	< = 2	S
Linezolid	2	S
Daptomycin	0.5	S
Clindamycin	> 2	R
Minocycline	> 8	R
Rifampicin	< = 0.5	S

S susceptible, R resistant

Case presentation

A 2-year-old girl with congenital intracranial cysts underwent endoscope-assisted fenestration and shunt valve replacement surgery against cysto-peritoneal shunt dysfunction. The pregnancy was uneventful and the child was born normally at 3,214 g, 49.0 cm height, and 43.1 cm head circumference. She had congenital intracranial cysts and a cerebral malformation was detected by pathological examination at 8 days of age. A cysto-peritoneal shunt was inserted 1 month after birth.

Four days after the operation (day 1), she developed a fever and irritability. On physical examination, she was febrile, had a Glasgow Coma Scale of E3V5M6, and showed nuchal rigidity. The patient's laboratory data were white blood cell count, $13.7 \times 10^9/L$ and C-reactive protein, 19.4 mg/dL. CSF examination showed a cell count of 236 / μL ; total protein, 10.6 g/L; and glucose, 2.6 mmol/L. Gram staining of the CSF detected gram-positive cluster microorganisms. We initiated intravenous VCM. MRSA was isolated

from the CSF on day 2; the MIC of VCM was 2 $\mu g/mL$ (Table 1). The cysto-peritoneal 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 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 – 100 mg/kg/d. The median serum trough level was 13.7 mg/L (interquartile range [IQR]: 10.7 – 15.2 mg/L), and the median CSF trough level was 5.3 mg/L (IQR: 4.1 – 5.9 mg/L), and the median CSF/serum concentration ratio was 0.29 mg/L (IQR: 0.28 – 0.42 mg/L). Her serum creatinine levels showed a normal range during treatment.

On day 3, her symptoms improved. CSF culture was no MRSA growth shown on day 6. 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 patient was discharged without any complications on day 42.

Discussion

We successfully treated cysto-peritoneal shunt-related infection caused by MRSA with MIC of VCM of 2 $\mu g/mL$ by monitoring both CSF and serum concentration levels of VCM. The penetration rate of VCM from the blood to CSF was shown to be sufficiently high.

The target concentration for CNS infection caused by MRSA with MIC of VCM of 2 $\mu g/mL$ could not be achieved based on the in vitro data [6]. However, the 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, 8–11].

There has been no clear evidence of the safety and efficacy levels of VCM concentration in CSF. However, based on the data from intraventricular administration, the CSF trough levels > 10 times the MIC have not been associated with severe or irreversible adverse events [1]. Concerning indicators of efficacy, the CSF trough concentration above the MIC has been suggested in pediatric patients [8].

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

	Day 4	Day 5	Day 6	Day 8	Day 9	Day 10	Day 12	Day 14	Day 17	Day 20
Serum (mg/L)	7.9	8.4	10.7	20.1	13.7	11.3	15.2	14.6		16.4
CSF (mg/L)			4.6	5.9	3.9			3.9	5.9	6.9
Serum / CSF			0.43	0.29	0.28			0.27		0.42
Dose (mg/kg/d)	80	90	100	75	75	75	72	72	72	70
Cre (mg/dL)	0.19		0.20	0.23	0.28	0.25	0.26	0.26		0.28

CSF cerebrospinal fluid, Cre creatinine

Table 3 Pharmacokinetics of vancomycin in pediatric patients with central nervous system infection

Study number	Study place	Number of patients	Age	Dosage of VCM	Concentration in CSF	CSF/serum (%)	Reference, first author (year)
1	USA	6	11 years (mean)	10–20 mg/kg, every 6–12 h	2.48 (mean)	0.77–18 (rang)	Laney Jorgenson (2007)
2	South Africa	9	15 months (mean)	15 mg/kg, every 6 h	3.3 (mean)	21 (mean)	K P Klugman (1995)
3	USA	3	26–31 weeks of gestation (range)	20 mg/kg, every 18–24 h	2.2–5.6 (range)	26–68 (rang)	Review P D Reiter (1996)
4	USA	8	4.3 years (median)	19 mg/kg, every 8 h (median)	1.07 (median)	8 (median)	Julie Autmizguine (2014)
5	Japan	1	2 years	70–100 mg/kg/d (range)	5.3 (median)	29 (median)	

CSF cerebrospinal fluid, VCM vancomycin

The penetration rate has been reported in the range of 0–68% in children (Table 3) [12–15]. A higher penetration rate by opening of the tight junctions of the blood–brain-barrier cells, delayed drug removal by a decrease of the CSF bulk flow, and inhibited activity by efflux pump of antibiotics have been occurred during the acute phase of bacterial meningitis [6, 7, 15, 16]. Otherwise, intense inflammation was not regularly present in cerebral ventricular shunt-related infections [7, 17]. 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 [14, 18–20].

Several studies have reported that intraventricular use of VCM may improve treatment outcomes without severe side effects in adult patients [21–23]. However, arecent systematic review noted insufficient evidence in pediatric patients, and intraventricular antimicrobial therapy is considered when clinical improvement is poor with intravenous administration alone [24].

In our patient, although the strain isolated from the CSF showed MIC of VCM of 2 µg/mL, successful treatment with intravenous VCM was achieved by monitoring the concentration in both the serum and CSF. The penetration rate was sufficiently high and the CSF trough levels were above the MIC during treatment.

High serum VCM concentration can cause complications such as nephrotoxicity, ototoxicity, and vasculitis [4]. We could avoid unnecessary dose increases by monitoring the CSF concentration, which may lead to excellent tolerance and no clinically significant adverse events.

In conclusion, monitoring the VCM concentration in the CSF and its serum concentration as indicators may help make decisions about the optimal dosage, changing second-line drugs, and reducing the frequency of side effects.

List of abbreviations CNS: Central nervous system; CSF: Cerebrospinal fluid; EVD: External ventricular drain; IQR: Interquartile range; MRSA: Methicillin-resistant *Staphylococcus aureus*; MIC: Minimal inhibitory concentration; TDM: Therapeutic drug monitoring; VCM: Vancomycin

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.

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

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 the parents of the patient.

Conflict of interest The authors declare that they have no conflict of interests.

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