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Research

High Concentration of Vancomycin in Children with Central Diabetes Insipidus: A Retrospective Case Series

Fumihiro Ochi[1*], Hisamichi Tauchi[1], Hiroshi Kimura[2], Junpei Hamada[1], Mayo Ueda[1], Toshihiro Jogamoto[1], Kozo Nagai[1], Minenori Eguchi-Ishimae[1], Mariko Eguchi[1]

[1]Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Ehime, Japan; [2]Division of Pharmacy, Ehime University Hospital, Toon, Ehime, Japan

ABSTRACT

Although high concentration of vancomycin (VCM) has the potential to cause acute kidney injury and ototoxicity, there were no studies focused on its pharmacokinetics in children with central diabetes insipidus (CDI). We therefore evaluated the pharmacokinetic indices of VCM in children with CDI diagnosed and treated at Ehime University Hospital between January 2008 and December 2019. Five patients with CDI administered VCM, were retrospectively reviewed. VCM median initial dose, trough value, clearance (CL) and half-life ($t_{1/2}$) were 42.0 mg/kg/day (range, 18.8-60.0 mg/kg/day), 34.5 mg/L (range, 12.5-182 mg/L), 6.54 mL/min (range, 1.57-47.1 mL/min), and 7.11 hr (range, 3.35-38.5 hr), respectively. VCM trough values were high in Patients of untreated or inadequately treated CDI. Our results suggest that the decrease in CL and the increase in volume of distribution caused by CDI and sepsis could result in an extended VCM $t_{1/2}$ and a higher VCM trough value in patients with CDI.

Keywords: Therapeutic drug monitoring; Vancomycin; Diabetes insipidus; Sepsis; Pediatric medication

Abbreviations: VCM: Vancomycin; CDI: Central Diabetes Insipidus; MIC: Minimum Inhibitory Concentration; CL: Clearance; $t_{1/2}$: Half-life; MRSA: Methicillin-Resistant *Staphylococcus aureus*; TDM: Therapeutic Drug Monitoring

INTRODUCTION

Vancomycin (VCM) is a glycopeptide antibiotic used for empiric therapy against hospital-acquired infections or severe infections caused by susceptible strains of gram-positive organisms, including Methicillin-Resistant *Staphylococcus aureus* (MRSA) [1]. However, vancomycin has the potential to cause considerable acute kidney injury or ototoxicity in children, particularly when steady-state concentrations (trough levels) of 15 mg/L to 20 mg/L are targeted for invasive MRSA infection [2].

The guideline for Therapeutic Drug Monitoring (TDM) associated with VCM therapy aims to optimize efficacy and reduce toxicity and resistance. In particular, TDM is indispensable under special circumstances such as high-dose VCM administration, severe infection, renal dysfunction, obesity or low-weight, and burns, when distribution volume is difficult to predict [3]. It is, therefore, necessary to consider the infection site, disease severity, patient weight, renal function, and pathogen susceptibility to determine the appropriate dose of VCM required.

On the other hand, there were no studies focused on the pharmacokinetic indices of VCM in children with Central Diabetes Insipidus (CDI). CDI is characterized by deficient synthesis or secretion of antidiuretic hormone. Patients with untreated CDI typically present with polyuria, nocturia, and polydipsia, due to the initial elevation in serum sodium and osmolality. In children with CDI, the water balance tends to be negative, and the pharmacokinetic parameters can fluctuate significantly [4,5].

At first, we hypothesized that the clearance of VCM has been higher in children with CDI. However, we found different effects. In this study, we, therefore, analyzed the pharmacokinetics of VCM in five children with CDI.

Correspondence to: Fumihiro Ochi, Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Ehime, Japan, E-mail: fmochi2000@yahoo.co.jp

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MATERIALS AND METHODS

This was a Case series. A total of 5,346 children were treated at Ehime University Hospital between January 2008 and December 2019. Among them, five patients with CDI administered VCM, were retrospectively reviewed. The process whereby children were selected for our study is shown in Figure 1.

Several clinical parameters were analyzed in each patient including age, sex, underlying disease, associated pathogen, use of a mechanical ventilator, presence of a central venous catheter, additional medications administered (furosemide or arginine vasopressin), laboratory data, as well as VCM dose, serum trough concentration, clearance and elimination half-life ($t_{1/2}$), and side effects. The pharmacokinetics of VCM was estimated by the Bayesian method [6].

Bacterial isolates were identified using standard bacteriological methods and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [7]. Antimicrobial susceptibility analysis of bacterial isolates was routinely performed using the broth microdilution method [8]. Susceptibility was assessed according to the guidelines of the Clinical and Laboratory Standards Institute.

When severe infection caused by gram-positive organisms was suspected from clinical symptoms or laboratory data, the pharmacist intervened in the initial dose planning using VCM TDM software (SHIONOGIVCM-TDM S-edition ver. 2009, Shionogi Inc., Japan) [9] and a continuous infusion of VCM was administered. The steady-state serum concentrations of VCM (trough concentrations) were measured within 30 min prior to the administration.

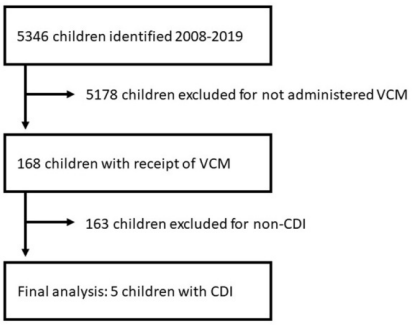

Figure 1: Flow diagram of reviewed patient.

RESULTS

Table 1 summarizes the clinical and laboratory findings of the five children with CDI. There were three males and two females. The median age was 31 months (range, 6 months to 11 years). The underlying disease was encephalopathy (n=2), intracranial hemorrhage (n=1), or brain tumor (n=2).

Two patients presenting with polyuria, developed hypernatremia after VCM administration (Patients 2 and 3). Arginine vasopressin was used to treat three CDI patients (Patients 1, 4, and 5). However, the dose was insufficient in two patients (Patients 1 and 4), due to poor parental medication adherence. All patients required central venous catheterization, and the three patients with either encephalopathy or brain hemorrhage, needed mechanical ventilation. As shown in Table 1, the indications for VCM were brain abscess, bacteremia, pneumonia, and febrile neutropenia. The identified pathogens were MRSA (n=2) and *Corynebacterium striaum* (n=1). All isolates exhibited beta-lactam resistance. In two patients, pathogens were not identified. The VCM minimum inhibitory concentration for C. *striatum* was 0.5 μg/mL, while that of MRSA was less than 1 μg/mL.

The median initial dose of VCM was 42.0 mg/kg/day (range, 18.8 mg/kg/day-60.0 mg/kg/day). The VCM median trough value, clearance (CL), and $t_{1/2}$ were 34.5 mg/L (range, 12.5 mg/L-182 mg/L), 6.54 mL/min (range, 1.57 mL/min-47.1 mL/min), and 7.11 hr. (range, 3.35 hr-38.5 hr.), respectively. VCM trough values were higher in Patients of untreated or inadequately treated CDI. Side effects were observed only in one Patient. This participant (Patient 2), developed transient renal dysfunction.

DISCUSSION

Our data indicate that high serum VCM concentration may potentially occur in some patients receiving appropriate VCM dosing, although a high serum VCM due to accidental overdose has been reported in pediatric patients [10]. Accordingly, even if the proper dose of VCM was used, it resulted in unexpectedly high trough values in patients with heart disease, dehydration, and caused deterioration of their general condition [11-13]. Therefore, caution is required in some patient groups, specifically if there any pathological changes are detected in the patient's condition throughout the treatment period. Our data supported in agreement with these previous observations.

Broome et al. reported that the $t_{1/2}$ of VCM ranged from approximately 2 hours to 10 hours depending on age. The VCM $t_{1/2}$ was 6 hours to 10 hours in the neonate, 4 hours in children 3 months to 4 years old, and 2.2 hours to 3 hours in children older than 4 years old, respectively [14]. In our study, the median VCM $t_{1/2}$ was 8.18 hours (range, 3.35 hours-38.5 hours) and 4 patients with CDI (excluded Patient 5) showed prolonged VCM $t_{1/2}$. Pediatric $t_{1/2}$ varies, because of its dependence on CL and volume of distribution (Vd), which depend on age, body weight, and serum creatinine value [15]. Sridharan et al. [16] reported that Vd was significantly higher in infants, with a decreasing trend in toddlers, children, and older children at a steady state. Additionally, children with renal dysfunction had lower CL and more prolonged $t_{1/2}$ compared with patients with normal renal clearance [16-18]. Therefore, tailor-made dosing is required in children, based on an evaluation of VCM Vd, CL, and $t_{1/2}$.

Table 1: Clinical and laboratory findings of patients with CDI.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, Sex	4 yr, male	6 mo, female	11 mo, female	11 yr, male	1 yr 2 mo, male
Height, Body weight	79 cm, 14.3 kg	63.5 cm, 6.5 kg	N/A, 10.1 kg	146 cm, 53 kg	70.8 cm, 8 kg
Underlying disease	HIE, CDI	IH, CDI	AE, CDI	brain tumor, CDI	brain tumor, CDI
Infection	brain abscess	bacteremia, SSI	VAP	FN	FN
Pathogen	C. *striatum*	MRSA	MRSA	unidentified	unidentified
Mechanical ventilator	+	+	+	–	–
CVC	+	+	+	+	+
Treatment					
Antibiotics	MEPM+VCM	VCM	MEPM+VCM	MEPM+VCM+MCFG	MEPM+VCM
AVP	insufficient	–	–	insufficient	+
Furosemide	–	+	–	+	+
Laboratory findings					
Alb (g/dL)	1.9	2.9	2.8	2.8	3.8
BUN (mg/dL)	9	34	47	19	5
Cre (mg/dL)	0.3	0.39	0.29	0.8	0.31
Na (mmol/L)	141	162	153	137	143
AVP (pg/mL)	0.7	1	1	<0.3	1.3
VCM trough (mg/L)	57.3	34.5	182	20	12.5
VCM initial dose	12.5 mg/kg/dose, 3 times/day	15.3 mg/kg/dose, 3 times/day	14.0 mg/kg/dose, 3 times/day	9.40 mg/kg/dose, 2 times/day	15.0 mg/kg/dose, 4 times/day
Clearance (mL/min)	6.54	5.57	1.57	47.1	14.5
$t_{1/2}$ (hr)	13	7.11	38.5	6.88	3.35
Side effect	–	AKI	–	–	–

AE, acute encephalopathy; AKI, acute kidney injury; AVP, arginine vasopressin; CDI, central diabetes insipidus; CVC, central venous catheter; FN, febrile neutropenia; HIE, hypoxic ischemic encephalopathy; IH, intracranial hemorrhage; MCFG, micafungin; MEPM, meropenem; mo, month; MRSA, methicillin-resistant Staphylococcus aureus; N/A, not available;SSI, surgical site infection; VAP, ventilator associated pneumonia; VCM, vancomycin; yr, year.

In addition, Patel et al. [19] reported mean trough concentration of VCM of 11.6 mg/L (range, <2.0 mg/L-39.7 mg/L) in children, with an average patient age of 6.5 years, and average initial dose of 52.55 mg/kg/day (range, 19.05 mg/kg/day-86.54 mg/kg/day) [19]. On the contrary, the median trough value of VCM in the five children with CDI in our study was greater, at 34.5 mg/L (range, 12.5 mg/L-182 mg/L), and the VCM trough values were high in 3 out of 5 patients (Patients 1 to 3). Interestingly, VCM trough value became elevated in patients 2 and 3, at the point when they developed CDI. Also, treatment for CDI was insufficient or absent in patients 1 and 4. Conversely, in patient 5, who received an appropriate arginine

vasopressin dose, the VCM trough value remained within the normal range. These clinical findings suggest that the pathological condition of CDI may have influenced the pharmacokinetics of VCM.

For example, CDI is characterized by decreased release of antidiuretic hormone (also called arginine vasopressin), resulting in a variable degree of polyuria [4,5]. Although VCM CL is expected to increase due to greater urine volume in patients with CDI, VCM CL decreased, and $t_{1/2}$ was also significantly prolonged. Polyuria may lead to intravascular dehydration, resulting in decreased renal blood flow with decreased glomerular filtration rate and therefore CL. Similarly, increased vascular permeability due to sepsis results in increased Vd and intravascular dehydration [20,21]. Accordingly, the decrease in CL and the increase in Vd could result in an extended VCM $t_{1/2}$ and a higher VCM trough value in patients with CDI.

The limitations of our study include its retrospective nature and the fact that it was conducted at a single center, and small sample size. As the administration of VCM to patients with CDI is rare, it will be necessary to accumulate patients for comparison with non-DI patients over time.

CONCLUSION

Our study suggests the need for caution regarding VCM concentration in patients with CDI because their blood concentration may be abnormally high even after the administration of the usual dose of VCM. Differences in pharmacokinetics may be an important consideration, to develop the best dosing for each pediatric patient.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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