Department of Pharmacy[1] and Infection Control Room[2], University of the Ryukyus Hospital; Department of Infectious, Respiratory, and Digestive Medicine[3], Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

Applicability of hemodialysis clearance parameter for vancomycin therapeutic drug monitoring during continuous hemodiafiltration in an infant

H. Shiohira[1,2,*], S. Isagawa[1], S. Yamada[1], S. Sunagawa[1], M. Nakamatsu[2,3], F. Yonaha[1], N. Hokama[1], J. Fujita[2,3], K. Nakamura[1]

Received September 4, 2018, accepted September 28, 2018

**Corresponding author: Hideo Shiohira, Ph.D., Department of Pharmacy, University of the Ryukyus Hospital. 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan*
apotheker-43@umin.ac.jp

Pharmazie 73: 737–739 (2018) *doi: 10.1691/ph.2018.8748*

Cases requiring vancomycin administration planning in infants undergoing continuous hemodiafiltration (CHDF) are extremely rare. Here, we report a single case in which vancomycin therapeutic drug monitoring and administration planning were implemented for an infant requiring CHDF. The patient was diagnosed with wound infection after gastrostomy and enterotomy surgery and received vancomycin treatment for infection with methicillin-resistant *Staphylococcus epidermidis*. The vancomycin trough serum concentration was successfully controlled within the acceptable range. Additionally, we discuss the potential usefulness of applying the CHDF clearance parameter for the fine management of vancomycin serum concentration in a pediatric patient undergoing CHDF.

1. Introduction

Vancomycin (VCM) is a glycopeptide antibiotic primarily used to treat Gram-positive infections caused by methicillin-resistant Staphylococci or ampicillin-resistant Enterococci. Because VCM blood trough concentrations are closely related to both clinical outcomes and the toxic effect of the drug, therapeutic drug monitoring (TDM) is recommended for maintaining an adequate trough concentration range in adult (Rybak et al. 2009) and pediatric patients (Miller et al. 2018). It is known that the half-life of VCM lengthens significantly in patients with renal insufficiency (Trotman et al. 2005). Therefore, it is important to monitor VCM trough concentrations to reduce nephrotoxicity in patients receiving aggressive dose targeting to VCM trough serum concentrations of 15–20 mg/L or who are at risk of toxicity, such as adult patients receiving concurrent treatment with nephrotoxins (Rybak et al. 2009).

Continuous hemodiafiltration (CHDF), which is a method of continuous renal replacement therapy (CRRT), is frequently used to treat patients who are critically ill with acute renal failure or chronic renal failure. Many reports of VCM TDM during CHDF in adults have been published. However, to the best of our knowledge, there has been no report of any infant cases of VCM TDM and administration planning during CHDF.

Here, we report an infant case of VCM TDM in which the patient received CHDF, and we discuss the adaptation availability of CHDF clearance parameters for VCM administration planning. This work was approved by the Ethics Committee of the University of the Ryukyus.

2. Case report

A 1-month-old female infant weighing 3.0 kg was diagnosed with neonatal asphyxia. CHDF and mechanical ventilation had been initiated when she was 2 days old. Additionally, due to the diagnosis of an underlying gastrointestinal perforation, gastrostomy and enterostomy surgery had been performed when she was six days old. After surgery, cefotiam (CTM) at a dose of 100 mg every (q) 8 h was initiated on suspicion of wound infection. At 16 days old, methicillin-resistant *Staphylococcus epidermidis* (MRSE) were detected by a culture test of the wound drain fluid. The Table shows the Clinical & Laboratory Standards Institute (CLSI) standards classified minimum inhibitory concentrations (MICs) of detected the MRSE; the VCM MIC was 1 µg/ml. At 31 days old, the patient's antibiotics were changed from CTM to VCM at a dose of 22 mg q24 h, and TDM was performed on the 34th day of life. The first TDM measurement revealed a VCM trough serum concentration value of 1.8 µg/ml (Fig.). We set the target range for the VCM trough serum concentration at 10–15 µg/ml and then increased the VCM dose to 40 mg q12 h. The second TDM measurement was performed at day 37; at this time, the VCM trough serum concentration was 17.0 µg/ml. Because the VCM serum concentration was assessed as being within the acceptable range, the same VCM dosing regimen was continued. A follow-up TDM performed at day 41 revealed a VCM trough serum concentration value of 17.8 µg/ml, still within the acceptable range. VCM treatment was stopped when the patient was 46 days old, and wound cultures at day 49 yielded negative results. The CHDF condition during the VCM treatment is shown in the Fig., and the patient's serum creatinine value was maintained at almost 0.1–0.2 mg/dL.

3. Pharmacokinetic considerations

During CHDF, the blood flow rate (QB) exceeds both the dialysate flow rate (QD) and the replacement flow rate (QF). Therefore, the drug clearance (CL_{CHDF}) approximates the diafiltrate rate (QD + QF). The drug clearance during CHDF is expressed by the product of the diafiltrate rate and the sieving co-efficient (SC) as shown in the following equation:

$CL_{CHDF} \simeq (QD + QF) \times SC$ (Hirata and Furukubo 2017).

The VCM protein binding rate was reported as being 34 % (Nakashima et al. 1992); therefore, the unbound drug fraction (fu) of 66 % was used as the sieving coefficient. The CHDF parameters of our patient were 0.15 L/h for QD and 0.03 L/h for QF. Based on these considerations, the CL_{CHDF} at the initial TDM measurement performed when the patient was 34 days old was obtained as shown below:

$CL_{CHDF} \simeq (0.15 \text{ L/h} + 0.03 \text{ L/h}) \times 0.66 = 0.119 \text{ L/h}$

The volume of distribution (Vd) for the patient was calculated using the Japanese infant Vd of 0.499 L/kg, yielding a value of

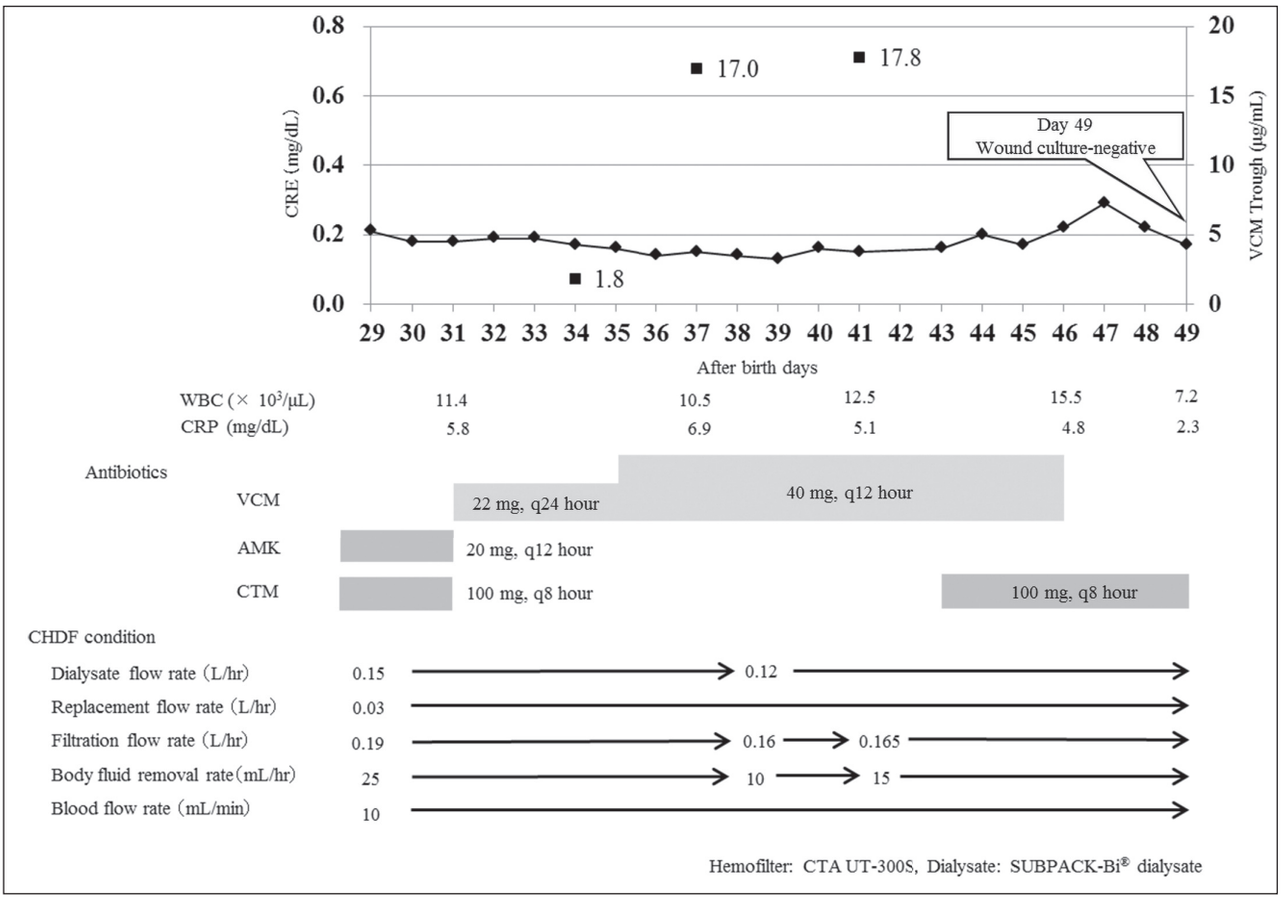

Fig.: The clinical course of the patient. CRE: serum creatinine (closed rhombus), VCM: vancomycin (closed square), WBC: white blood cell, CRP: C-reactive protein, AMK: amikacin, CTM: cefotiam, CHDF: continuous hemodiafiltration. The SUBPACK-Bi® dialysate (NIPRO Corp., Osaka, Japan) contained: Na, 140 mEq/L; K, 2.0 mEq/L; Cl, 113. mEq/L; Ca^{2+}, 3.5 mEq/L; and HCO_3, 35 mEq/L. The CHDF conditions fluctuated during VCM treatment, but the blood flow rate exceeded both the dialysate flow rate and replacement flow rate in all periods.

1.74 L for our patient (Imano et al. 2003). The elimination rate constant (ke) and half-life ($t_{1/2}$) were then determined from the obtained CL as follows:

CL (L/h) = ke (h^{-1}) × Vd (L) (Ambrose and Winter 2009)

ke (h^{-1}) = CL (L/h)/Vd (L) = (0.119 L/h)/(1.74 L) = 0.068 h^{-1}

$t_{1/2}$ (h) = 0.693/ke (h^{-1}) = 10.2 h

Here, the target peak concentration was 25–40 μg/ml (average: 32.5 μg/ml), the trough concentration was 15 μg/ml, and the average concentration (Cp) was 23.8 μg/ml. The appropriate maintenance dosing regimen and daily dose of VCM were calculated from the CL and $t_{1/2}$ using the following equation:

Dose (mg) = Cp (μg/ml) × CL (L/h) × t (h) (Ambrose and Winter 2009)

= 23.8 μg/ml × 0.119 L/h × 24 h

= 68 mg/day.

It was assumed that a suitable dosing interval is approximately one $t_{1/2}$ from the target peak concentration (32.5 μg/ml). Therefore, the optimized regimen was set as 34 mg q12 h. The VCM $t_{1/2}$ in neonates and infants was reported as 4.9–6.6 h (McDougal et al. 1995; Pacifici and Allegaert 2012), and a VCM dosing regimen of 15 mg/kg q12 h is recommended for neonates with normal renal function (Capparelli et al. 2001; Pacifici and Allegaert 2012). In the present case, the calculated $t_{1/2}$ of the patient was 10.2 h, which is prolonged compared with that in neonates and infants with normal renal function. Therefore, we considered that the initial target trough range (10–15 μg/ml) could be achieved by the calculated regimen (34 mg per 12 h).

In fact, the VCM trough serum concentrations of 17–17.8 μg/ml were actually observed when we administered a 40 mg per 12 h as VCM regimen, it was considered slightly overdosing.

4. Conclusion

In conclusion, this single case of an infant undergoing CHDF suggests that VCM TDM and the implementation of VCM administration planning could successfully control the VCM trough serum concentration, keeping it within acceptable levels. Furthermore, VCM administration planning based on the CHDF clearance would be useful for the fine management of VCM serum concentration in CHDF enforcement.

Acknowledgments: We thank Katie Oakley, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Conflicts of interests: none declared

References

Ambrose PJ, Winter ME (2009) Vancomycin. In: Winter ME (ed.) Basic clinical pharmacokinetics., 5th ed., Philadelphia, p. 459 – 487.

Capparelli EV, Lane JR, Romanowski GL, McFeely EJ, Murray W, Sousa P, Kildoo C, Connor JD (2001) The influences of renal function and maturation on vancomycin elimination in newborns and infants. J Clin Pharmacol 41: 927 – 934.

Hirata S, Furukubo T (2017) Guidebook for drug in dialysis patients, 3rd ed., Tokyo, p. 85 – 136. Japanese.

Imano H, Ueno K, Ikura M, Yoshimura H, Mitsutake K (2003) Development of a dosage guideline based on vancomycin pharmacokinetics. Jpn J Chemother 51: 87 – 90. Japanese with English abstract.

Table: Drug susceptibility of detected Methicillin-Resistant *Staphylococcus epidermidis* (MRSE)

Antibiotics	MIC (μg/mL)	Susceptibility
MPIPC	≧4	R
PCG	≧0.5	R
CEZ	≦4	R
IPM	≦1	R
CMZ	32	R
EM	≧8	R
ABPC/SBT	4	R
CLDM	≦0.25	S
AMK	8	S
VCM	1	S
ABK	≦1	S
LVFX	4	R
GM	≧16	R
MINO	≦0.5	S
TEIC	16	I
LZD	2	S
FOM	≧128	R
DAP	0.5	S

MPIPC: oxacillin, PCG: penicillin G, CEZ: cefazolin, IPM: imipenem, CMZ: cefmetazole, EM: erythromycin, ABPC/SBT: ampicillin/sulbactam, CLDM: clindamycin, AMK: amikacin, VCM: vancomycin, ABK: arbekacin, LVFX: levofloxacin, GM: gentamicin, MINO: minocycline, TEIC: teicoplanin, LZD: linezolid, FOM: fosfomycin, DAP: Daptomycin.

McDougal A, Ling EW, Levine M (1995) Vancomycin pharmacokinetics and dosing in premature neonates. Ther Drug Monit 17: 319 – 326.

Miller CL, Winans SA, Veillette JJ, Forland SC (2018) Use of individual pharmacokinetics to improve time to therapeutic vancomycin trough in pediatric oncology patients. J Pediatr Pharmacol Ther 23: 92 – 99.

Nakashima M, Katagiri K, Oguma T (1992) Phase I studies on vancomycin hydrochloride for infection. Chemotherapy 40: 210 – 224. Japanese with English abstract.

Pacifici GM, Allegaert K (2012) Clinical pharmacokinetics of vancomycin in the neonate: a review. Clinics 67: 831 – 837.

Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP (2009) Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49: 325 – 327.

Trotman RL, Williamson JC, Shoemaker DM, Salzer WL (2005) Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis 15: 1159 – 1166.