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Influence of cerebral fluid drainage on the pharmacokinetics of vancomycin in neurosurgical patients

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The objective of this study was to retrospectively investigate the influence of cerebral fluid drainage on the serum concentrations and pharmacokinetic parameters of vancomycin (VCM). We analyzed 55 patients with normal renal function who had been hospitalized in the neurosurgical ward and received intravenous infusions of VCM. We compared the daily doses of VCM, serum VCM concentrations, serum concentration/dose ratio (C/D ratio), and pharmacokinetic parameters calculated using the Sawchuk–Zaske method between patients who underwent cerebral fluid drainage (drainage group) and controls (non-drainage group). The patients in the drainage group showed a significantly lower trough concentration of VCM (5.8 ± 3.3 μg/mL) than that shown by the non-drainage group (9.9 ± 5.4 μg/mL, $p = 0.017$). Further, the patients in the drainage group showed a significantly lower trough C/D ratio (0.32 ± 0.17) than that shown by the non-drainage group (0.50 ± 0.31, $p = 0.047$). In conclusion, cerebral fluid drainage may influence VCM pharmacokinetics. Our findings strongly suggest that a high dose of VCM is required to maintain optimal serum concentrations of VCM in patients managed with cerebral fluid drainage.

1. Introduction

Vancomycin (VCM) belongs to the group of glycopeptide antibiotics and is effective against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Therapeutic drug monitoring of VCM is recommended from the first stage of administration, because serum VCM concentrations are correlated with its efficacy and safety (Matzke et al. 1986; Rybak et al. 2009; Lodise et al. 2009; Kullar et al. 2011). The pharmacokinetics of VCM are affected by renal function, because 90% of VCM is excreted into the urine as the unchanged drug (Matzke et al. 1986). Therefore, the renal function of patients should be considered when designing the dosage regimen (Moellering et al. 1981; Matzke et al. 1984; Yasuhara et al 1998).

Cerebral fluid drainage is one of the neurosurgical treatments for delayed cerebrovascular spasm and for removal of hematomas and cerebrospinal fluid (CSF) to decrease intracranial pressure. In addition, cerebral fluid drainage is used for the treatment of acute hydrocephalus and meningitis. We observed that administration of a high dose of VCM was required for patients managed with cerebral fluid drainage. Pujal et al (2006). showed that patients with an external ventricular shunt require high VCM doses because of greater VCM clearance. The influence of cerebral fluid drainage on the pharmacokinetics of VCM is poorly understood, because to date, few studies have investigated this aspect. This study aimed to investigate the influence of cerebral fluid drainage on the serum concentrations and pharmacokinetics of VCM.

2. Investigations and results

2.1. Patient background

Demographic characteristics were compared between the patients in the drainage group ($n = 10$) and those in the non-drainage group ($n = 45$) (Table 1). No significant differences were observed in sex, age, Bw, SCr levels, CCr, albumin (Alb) levels, and total protein (TP) levels between the two groups.

2.2. Influence of cerebral fluid drainage on serum VCM concentrations

The initial dose of VCM showed no significant differences in the two groups (Table 2). The mean trough serum VCM concentration after administration of the initial dose in the drainage group, 5.8 ± 3.3 μg/mL, was significantly different from that in the non-drainage group, 9.9 ± 5.4 μg/mL ($p = 0.017$). The mean trough C/D ratios in the two groups were 0.32 ± 0.17 and 0.50 ± 0.31, which were significantly different ($p = 0.047$, Fig. 1). The mean peak serum VCM concentration in the drainage group, 20.4 ± 4.6 μg/mL, was significantly different from that in the non-drainage group, 25.5 ± 5.6 μg/mL ($p < 0.001$). The corresponding mean peak C/D ratios were 0.32 ± 0.17 and 0.50 ± 0.31, which were marginally significant ($p = 0.073$, Fig. 2). However, because of an error in blood drawing, we analyzed the data of only 44 patients in the non-drainage group for peak concentration and C/D ratio.

Table 1: Patient background

	Non-drainage group (n = 45)	Drainage group (n = 10)	p value
Sex (m/f)	34/11	7/3	0.71 [a]
Age (years)	65.8 ± 13.1 (33–88)	63.4 ± 13.2 (32–77)	0.55 [b]
Bw (kg)	58.7 ± 10.7 (38.0–100.0)	59.2 ± 10.5 (47.0–75.0)	0.86 [b]
SCr (mg/dL)	0.60 ± 0.18 (0.36–1.04)	0.56 ± 0.29 (0.32–1.30)	0.16 [b]
CCr [*](mL/min)	103.5 ± 36.0 (60.3–227.8)	120.6 ± 36.3 (60.8–164.4)	0.14 [b]
CCr[**](mL/min)	88.5 ± 26.1 (60.1–158.4)	91.2 ± 26.2 (60.7–124.7)	0.80 [b]
Alb (g/dL)	2.38 ± 0.57 (1.4–3.5)	2.28 ± 0.55 (1.7–3.5)	0.74 [b]
TP (g/dL)	6.14 ± 0.94 (4.0–8.1)	6.08 ± 0.84 (5.2–8.0)	0.79 [b]

BW, body weight; SCr, serum creatinine; CCr, creatinine clearance; Alb, albumin; TP, total protein. Each value represents the mean ± standard deviation. *, calculated by Cockcroft–Gault formula; **, calculated by Cockcroft–Gault formula (corrected serum creatinine (SCr) < 0.6 mg/dL to a value of 0.6); [a], chi-square test; [b], Mann–Whitney *U*-test

Table 2: Initial vancomycin dosage

	Non-drainage group (n = 45)	Drainage group (n = 10)	p value
Initial Dosage (mg/day)	2050.0 ± 694.1 (1000–3500)	1850.0 ± 394.4 (1250–2500)	0.41 [a]
Initial Dosage (mg/kg/day)	35.6 ± 12.5 (15.6–77.8)	32.0 ± 8.0 (17.5–42.6)	0.41 [a]

Each value represents the mean ± standard deviation. [a], Mann-Whitney *U*-test

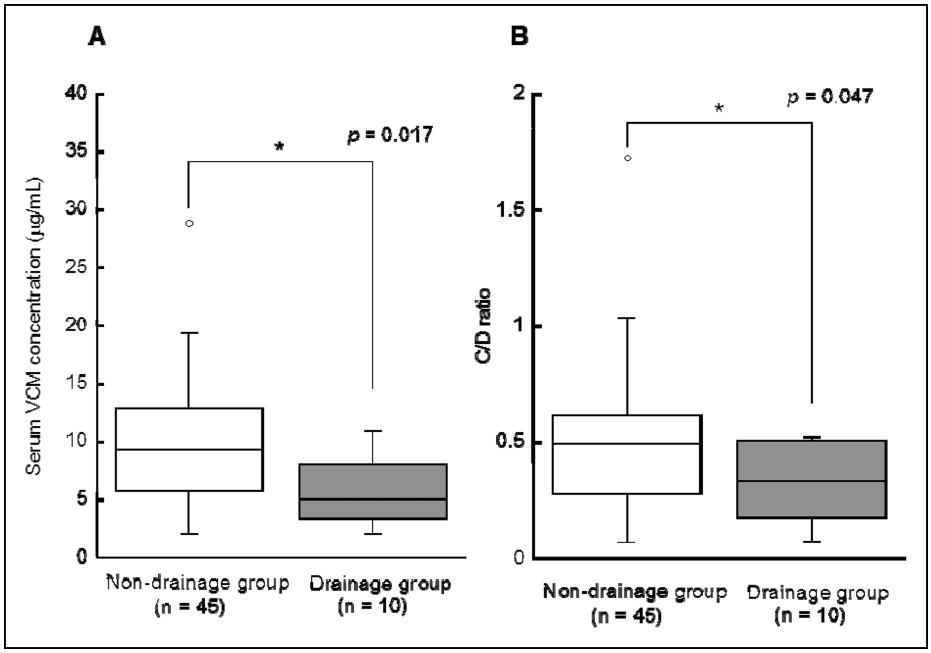

Fig. 1: Comparison of trough serum vancomycin concentrations (A) and concentration/dosage (C/D) ratio (B) after administration of an initial dosage between the drainage group and non-drainage group. P values were determined using the Mann–Whitney *U*-test.

Table 3: Adjusted dose of vancomycin

	Non-drainage group (n = 45)	Drainage group (n = 10)	p value
Redesigned Dosage (mg/day)	2355.6 ± 778.8 (1000–4500)	2700.0 ± 349.6 (2000–3000)	0.064 [a]
Redesigned Dosage (mg/kg/day)	41.3 ± 14.8 (16.7–84.9)	46.5 ± 8.0 (35.2–61.2)	0.099 [a]

Each value represents the mean ± standard deviation. [a], Mann-Whitney *U*-test

The adjustment in the VCM dose made on the basis of the serum VCM concentration after administration of the initial dose is shown in Table 3. The mean redesigned doses were 2700.0 ± 349.6 mg/day and 2355.6 ± 778.8 mg/day in the drainage and non-drainage groups, respectively, the difference between which was marginally significant (p = 0.064). The mean doses based on weight were 46.5 ± 8.0 mg/kg/day and 41.2 ± 14.8 mg/kg/day, the difference between which was also marginally significant (p = 0.099).

We measured serum VCM concentrations in 7 patients in the drainage group and 25 patients in the non-drainage group after adjustment of the dose of VCM. The mean trough serum VCM concentration was 10.5 ± 4.9 μg/mL in the patients in the drainage group and 12.0 ± 3.6 μg/mL in the patients in the non-

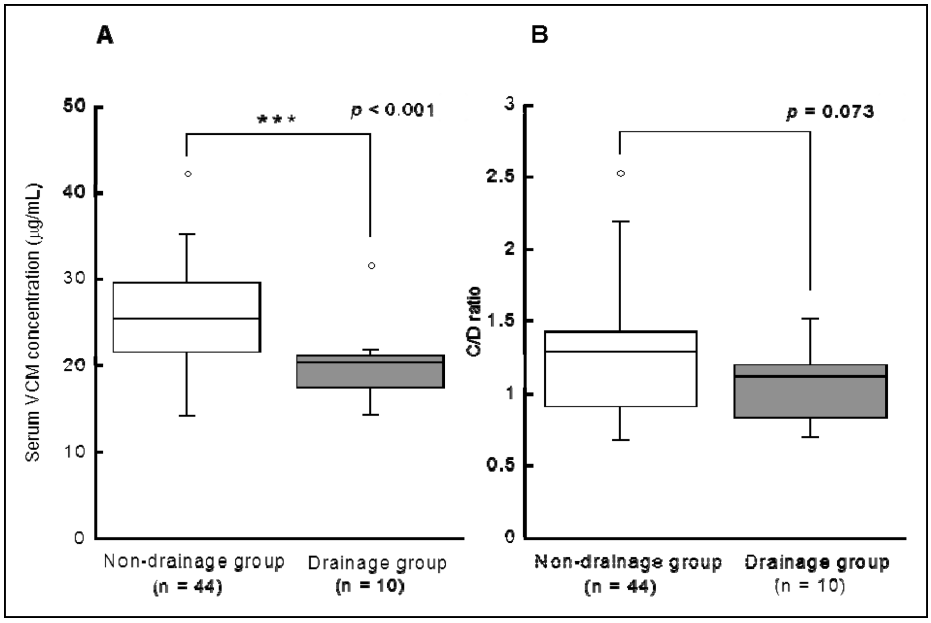

Fig. 2: Comparison of peak serum vancomycin concentrations (A) and concentration/dosage (C/D) ratio (B) after administration of an initial dose between the drainage group and non-drainage group. P values were determined using the Mann–Whitney *U*-test.

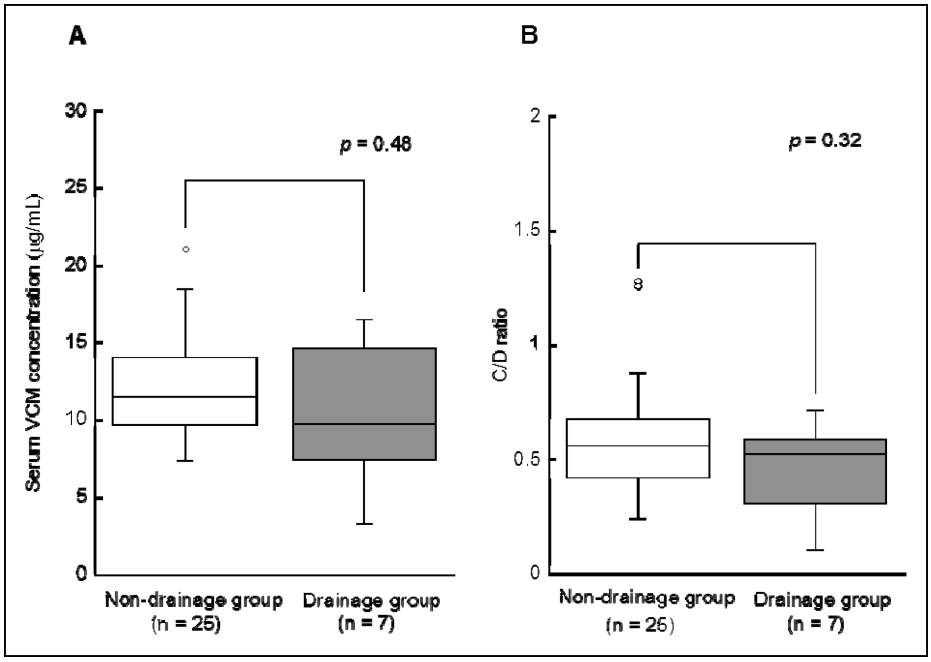

Fig. 3: Comparison of trough serum vancomycin concentrations (A) and concentration/dosage (C/D) ratio (B) after administration of an adjusted dose between the drainage group and non-drainage group. P values were determined using the Mann–Whitney *U*-test.

drainage group (p = 0.48), and the C/D ratios were 0.45 ± 0.22 and 0.59 ± 0.26 (p = 0.32), respectively, which were not significantly different. The mean peak serum VCM concentrations in the two groups were 27.5 ± 6.3 μg/mL and 26.7 ± 5.4 μg/mL (p = 0.78), and the C/D ratios were 1.15 ± 0.33 and 1.27 ± 0.32 (p = 0.53), respectively, which were not significantly different.

2.3. Influence of cerebral fluid drainage on the pharmacokinetic parameters of VCM

The estimated pharmacokinetic parameters of VCM calculated using the Sawchuk–Zaske method using serum VCM concentrations after administration of the initial dose are shown in Table 4. The mean CL_{VCM} in the drainage group and in the non-drainage group were marginally significant (p = 0.089). The mean V_d in the drainage and non-drainage groups were not significantly different (p = 0.503). The mean k_e in the two groups were marginally significant (p = 0.058). The mean $t_{1/2}$ values in the two groups were marginally significant (p = 0.063).

2.4. Influence of the amount of cerebral fluid drained on the serum VCM concentration

We measured the amount of cerebral fluid drained per day in 7 patients in the drainage group. No correlation was observed between the amount of cerebral fluid drained and the serum VCM concentration or C/D ratio.

3. Discussion

In this study, we investigated the influence of cerebral fluid drainage on the pharmacokinetics of VCM for patients man-

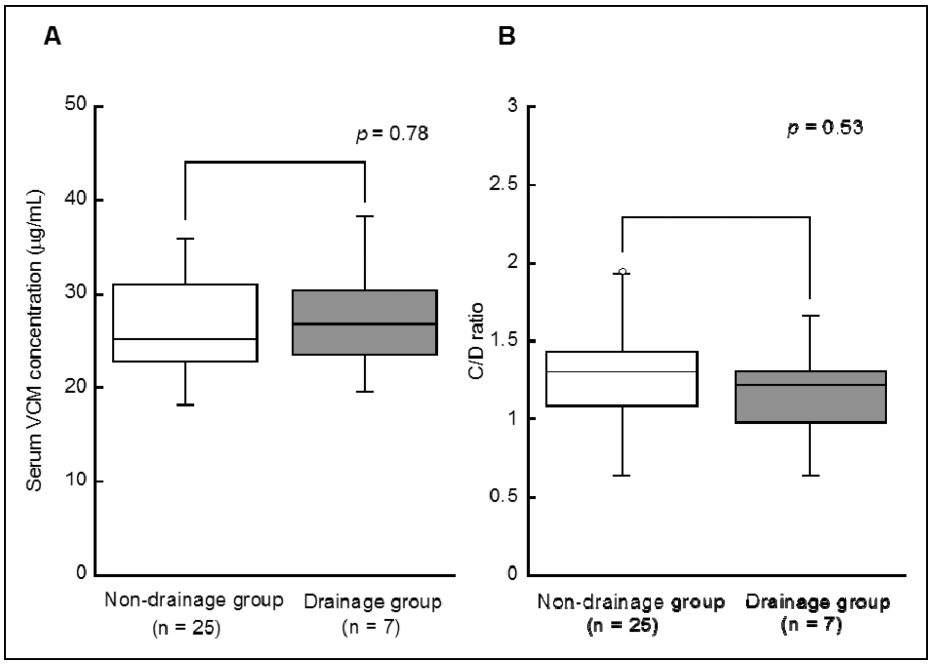

Fig. 4: Comparison of peak serum vancomycin concentrations (A) and concentration/dosage (C/D) ratio (B) after administration of an adjusted dose between the drainage group and non-drainage group. P values were determined using the Mann-Whitney *U*-test.

Table 4: Pharmacokinetic parameters of vancomycin

	Non-drainage group (n = 44)	Drainage group (n = 10)	p value
CL_{VCM} (L/h)	5.23 ± 1.71 (2.19–9.22)	6.67 ± 2.12 (3.97–11.33)	0.038 [a]
CL_{VCM} (L/h/kg)	0.091 ± 0.032 (0.039–0.168)	0.115 ± 0.044 (0.072–0.231)	0.089 [a]
V_d (L)	66.7 ± 17.2 (41.5–117.1)	63.8 ± 13.0 (37.2–88.3)	0.767 [a]
V_d (L/kg)	1.16 ± 0.30 (0.46–2.10)	1.10 ± 0.27 (0.78–1.54)	0.503 [a]
k_e (h^{-1})	0.083 ± 0.034 (0.027–0.164)	0.108 ± 0.039 (0.070–0.197)	0.058 [a]
$t_{1/2}$ (h)	9.9 ± 4.6 (4.2–25.3)	7.1 ± 2.2 (3.5–9.9)	0.063 [a]

CL, total clearance; V_d, distribution volume; k_e, elimination rate constant; $t_{1/2}$, elimination half-life. Each value is calculated using the Sawchuk–Zaske method and represents the mean ± standard deviation. [a], Mann–Whitney *U*-test

aged with continuous drainage of cerebral fluid and intravenous administration of VCM. We compared the initial and redesigned VCM dosage, serum concentration, C/D ratio, and pharmacokinetic parameters using the Sawchuk–Zaske method between the drainage group and a non-drainage group. The trough serum VCM concentration and C/D ratio after administration of the initial dose in the drainage group were significantly lower than those in the non-drainage group. Peak concentration after administration of an initial dose was significantly lower in the drainage group, and the peak C/D ratio in the drainage group was lower than that in the non-drainage group, but the intergroup differences were marginally significant. The redesigned dosage in the drainage group was higher than that in the non-drainage group, but the intergroup difference was marginally significant. CL_{VCM} and k_e in the drainage group were higher than the corresponding values in the non-drainage group, but the intergroup differences were marginally significant; however, no significant difference was observed in the V_d values of both groups. Therefore, we suggest that cerebral fluid drainage may affect the pharmacokinetics of VCM.

Pujal et al. (2006) reported that greater VCM clearance was observed in patients with an external ventricular shunt and that these patients required a daily dose of VCM that was 1.5 times higher than that in normal patients. Further, on the basis of the Bayesian method, the authors suggested that this increase in dose was because of the increase in VCM clearance and not because of the increase in distribution volume. We calculated the pharmacokinetic parameters using the Sawchuk–Zaske method rather than the Bayesian method, which uses population parameters, mainly because of two reasons. The subjects in this study were older, and their weights were lower than those of the subjects in the study by Pujal et al.; therefore, an accurate assessment of SCr and renal function could not be made using the Cockcroft–Gault formula. Further, we assumed that a patient managed with cerebral fluid drainage is under special clinical conditions. When we compared the pharmacokinetic parameters between the two groups, CL_{VCM} and k_e in the drainage group were higher than the corresponding values in the non-drainage group, but the intergroup differences were marginally significantly. However, no significant difference was observed in V_d between the two groups. Considering the marginal significance of the intergroup difference in the adjusted dose, the decrease in the serum VCM concentrations in this study may be because of an increase in VCM clearance, and not distribution volume. Our data appear to be consistent with those reported by Pujal et al.

VCM penetrates into the cerebral fluid, and CSF penetration significantly increases in the presence of meningeal inflammation (Matzke et al. 1986; Lutsar et al. 1998; Ahmed et al. 1999; Andes et al. 1999; Albanèse et al. 2000; Nau et al. 2010). The concentration-time curves in the serum and CSF do not run parallel; therefore, pharmacokinetic parameters in the CSF differ from those in the serum (Lutsar et al. 1998; Andes et al. 1999; Nau et al. 2010). The half-lives of hydrophilic agents (VCM and β-lactams) in the CSF tend to be extended, and the time

to achieve peak concentrations in the CSF is delayed (Lutsar et al. 1998). Typically, drugs are removed from the central nervous compartments *via* two pathways: (1) diffusion back into the blood through the blood-brain/blood-CSF barrier and (2) bulk flow of the interstitial fluid of the brain and CSF into the venous blood though the arachnoid granulations and cranial and spinal nerve roots (Nau et al. 2010). In this study, cerebral fluid drainage may become the third component of drug removal from the central nervous compartments and affect VCM clearance. However, no correlation was observed between the amount of cerebral fluid drained and the serum VCM concentrations. Penetration of antibiotics into the CSF is dependent on lipid solubility, molecular size, capillary and choroid plexus efflux pumps, protein binding, and the degree of inflammation (Lutsar et al. 1998; Andes et al. 1999; Nau et al. 2010). The degree of inflammation strongly influences the penetration of VCM into the CSF; however, there is great variability among the studies (Lutsar et al. 1998; Andes et al. 1999; Albanèse et al. 2000; LeRoux et al. 2003; Pfausler et al. 2003; Nau et al. 2010). Additionally, the concentration-time curves of VCM in the CSF vary according to the type of drainage (Wang et al. 2008). Therefore, one reason for the lack of correlation between the amount of cerebral fluid drained and the serum VCM concentrations was variation of penetration into the CSF. Further studies are required to calculate the extent of contribution of cerebral fluid drainage by measuring the VCM concentrations in the CSF and discharge of the cerebral fluid.

In the present study, we found that cerebral fluid drainage may affect the pharmacokinetics of VCM, because cerebral fluid drainage reduces the serum VCM concentrations and tends to increase VCM clearance. Additionally, patients managed with cerebral fluid drainage tend to require higher than normal doses of VCM. Our results suggest that cerebral fluid drainage is one of the factors that affects the pharmacokinetics of VCM. However, the extent of the impact of cerebral fluid drainage on VCM pharmacokinetics remains to be clarified. The pharmacokinetics of VCM can differ from the predicted pharmacokinetics in special clinical conditions. Therefore, it is important to design an appropriate dosage regimen by frequently measuring the serum VCM concentrations.

4. Experimental

4.1. Subjects

The subjects were patients who had been hospitalized in the neurosurgical ward at Kainan Hospital and received an intravenous infusion of VCM (Shionogi & Co., Ltd., Osaka, Japan) from January 2007 to December 2010. Patients with diminished renal function, as indicated by a creatinine clearance (CCr) below 60 mL/min, were excluded from this study. The Ccr was estimated using the Cockcroft–Gault formula (Cockcroft et al. 1976) as follows:

Men: Ccr (mL/min) = {[140 – age (years)] × body weight (Bw, kg)}/[72 × serum creatinine levels (SCr; mg/dL)]

Women: Ccr (mL/min) = 0.85 × {[140 – age (years)] × Bw (kg)}/[72 × SCr (mg/dL)]

However, we corrected the SCr < 0.6 mg/dL to 0.6 (Tanaka et al. 2006). Patients who were managed with an internal shunt or cerebral fluid drainage before measurement of serum VCM concentration were excluded. We included 55 patients who met the criteria. To investigate whether cerebral fluid drainage affected the pharmacokinetics of VCM, we divided the patients into two groups, the drainage group (n = 10) and the non-drainage group (n = 45), on the basis of whether they were managed with cerebral fluid drainage.

4.2. Method of VCM administration and measurement of serum VCM concentrations

To investigate whether cerebral fluid drainage affected serum VCM concentrations, we retrospectively compared the initial daily dose of VCM, serum VCM concentrations, and the ratio of serum concentrations and initial dose (C/D ratio) between the drainage group and non-drainage group. Additionally, we compared the daily adjustments in the VCM dosage made on the basis of serum VCM concentrations after administration of an initial dose. However, if the dosage regimen did not require amendment, we used the initial dose as a substitute for the daily adjustment in VCM dosage. Further, we compared the serum VCM concentration and C/D ratio after adjustment of VCM dosage. We obtained several blood samples at steady-state conditions from each patient during VCM treatment. The blood samples were drawn just before administering the dose (trough) and 1 h after initiation of drug infusion (peak). The initial dosage regimen was decided using the population mean method, and the dosage regimen was adjusted using the Bayesian method. The pharmacokinetic parameters estimated by Yasuhara et al. (1998) in a Japanese population were used for the population mean method and Bayesian method on the basis of a two-compartment model. The serum concentration of VCM was measured using a fluorescence immunoassay method (TDx-FLx analyzer; Abbott Japan Co., Ltd.) from January 2007 to July 2009 and using a chemiluminescent immunoassay method (ARCHITECT analyzer i1000 SR; Abbott Japan Co., LTD.) from August 2009 to December 2010. The lower limit of detection obtained using the TDX-FLx was 2.0 μg/mL and that obtained using the ARCHITECT analyzer *i*1000 SR was 0.42 μg/mL. If the serum VCM concentration decreased below measureable limits, we analyzed the concentration using the limit-of-detection concentration.

4.3. Method for determining the pharmacokinetic parameters of VCM

To investigate whether cerebral fluid drainage affects the pharmacokinetics of VCM, we compared the estimated pharmacokinetic parameters, namely VCM clearance (CL_{VCM}), volume of distribution (V_d), elimination rate constant (k_e), and half-life ($t_{1/2}$), between the two groups. These parameters were calculated using the Sawchuk–Zaske method (Sawchuk et al. 1976) on the basis of the serum VCM concentration of initial doses. We used the first blood samples (trough) as a substitute for the third blood samples (trough of next administration).

4.4. Relationship between the discharge of cerebral fluid and the serum VCM concentrations

To investigate whether the amount of cerebral fluid drained influenced the serum VCM concentrations, we calculated the Spearman rank-correlation coefficient between the amount of cerebral fluid drained per day and the serum VCM concentration and C/D ratio of initial dosage.

4.5. Statistical analysis

All the data are presented as mean ± standard deviation (S.D.). Statistical analyses were performed using KaleidaGraph 4.1 ver. Japanese (HULINKS, Inc.). The Mann-Whitney *U*-test was performed to compare the data from two different groups. Sex analysis was performed using the Chi-square test using Microsoft Excel (Microsoft Japan Co., Ltd.). The Spearman rank-correlation coefficient was calculated using IBM SPSS Statics (IBM Japan, Ltd.). A p value of < 0.05 was considered statistically significant.

4.6. Ethical considerations

This study complied with ethical guidelines for clinical research and was approved by the medical research ethical review board at Kainan Hospital and School of Pharmacy, Aichi Gakuin University. To protect patients' privacy, personal information was anonymized in a linkable fashion for the data analysis. Patients' personal information could not be identified, and there was no disadvantage to patients.

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