Case Reports in Neurology

Case Rep Neurol 2013;5:183–186

DOI: 10.1159/000355638
Published online: October 5, 2013

1662–680X/13/0053–0183$38.00/0
www.karger.com/crn

A Case of Severe Ganciclovir-Induced Encephalopathy

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Key Words
Ganciclovir · Encephalopathy · Kidney transplantation · Dialysis · Cytomegalovirus enteritis

Abstract
Background: Ganciclovir, a drug against cytomegalovirus (CMV) infection, is generally well tolerated, but can cause neurotoxicity such as encephalopathy. Although ganciclovir-induced encephalopathy has been described in several reports, a literature search revealed that ganciclovir concentrations in the blood or cerebrospinal fluid were previously measured in only 3 patients with encephalopathy. Symptoms usually include confusion and disturbed consciousness, which mimic CMV encephalitis. Prompt and accurate diagnosis is thus sometimes difficult, and is derived solely from accumulated clinical information of definite cases, since ganciclovir concentrations, not routinely measured, become available after several days or a few weeks. ***Case Presentation:*** Here, we summarize clinical information of all patients with definite ganciclovir-induced encephalopathy including our own patient, who had severe symptoms, with the highest reported trough concentration of ganciclovir in the blood, and underwent therapeutic dialysis with complete recovery. ***Conclusion:*** Our summary of patients with definite encephalopathy could lead to prompt and accurate diagnoses.

Introduction

Encephalopathy can be caused by neurotoxicity with prophylactically or therapeutically administered drugs such as acyclovir, ganciclovir, and their prodrugs, valacyclovir and

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valganciclovir [1]. The drugs are structurally similar nucleoside analogues, but their effects on neurons are poorly understood. Acyclovir-induced encephalopathy is more widely known than ganciclovir-induced encephalopathy, possibly because acyclovir is used against herpes virus infection, which is more common than cytomegalovirus (CMV) infection, for which ganciclovir is used. Ganciclovir was also reported to be effective against hepatitis B infection [2], but has rarely been used for this indication recently. Although ganciclovir-induced encephalopathy has been documented previously, a literature search revealed that ganciclovir concentrations in the blood or cerebrospinal fluid (CSF) have been reported in only 3 patients [1–3]. Previous reports on patients with such definite ganciclovir-induced encephalopathy have suggested that the trough concentration of ganciclovir in the blood is important [1]. Here, we summarize clinical information of patients with definite ganciclovir-induced encephalopathy including our own patient, who had severe symptoms, with the highest reported trough concentration of ganciclovir in the blood, and underwent therapeutic dialysis.

Case Presentation

A 55-year-old man started to receive hemodialysis because of diabetic renal failure 2 years previously. He underwent renal transplantation 1.5 years previously, and had been receiving immunosuppressants since then. Eight months after transplantation, the serum creatinine level increased to 4.4 mg/dl. He had CMV enteritis with occult blood in the stool and an elevated CMV pp65 (C7-HRP) antigen level in blood mononuclear cells. Intravenous ganciclovir (150 mg/day) was administered for 11 days, followed by valganciclovir (450 mg/day). Because the enteritis was very severe, ganciclovir and valganciclovir were not reduced to maintenance doses, which are generally half of starting doses. Two days after starting valganciclovir, he had unsteady gait, but could walk unaided. On the next day, the patient needed assistance with walking. His consciousness was mildly disturbed (E3, V5, and M6 on the Glasgow Coma Scale). One day later, he became delirious intermittently. Two days later, he was found on the floor after falling, without major injuries. He was suspected to be irritated and exhausted because of severe enteritis. Nine days after starting valganciclovir, his level of consciousness worsened (E3, V3, and M5), and he could not receive oral drugs, including valganciclovir. Neurologists were consulted. Encephalitis was unlikely, since no meningeal signs or fever was noted; the cell count was normal (0.33 cells/μl) in the CSF, and the protein concentration marginally elevated (54 mg/dl). CMV, herpes simplex virus, varicella-zoster virus, and Epstein-Barr virus DNA was later found to be negative in the CSF. Ganciclovir-induced encephalopathy was suspected, and the drug was withdrawn. Because of the risk of further falls, hemodialysis using a VPS-15HA membrane, a vitamin E-coated polysulfone membrane (Asahi Kasei Kuraray Medical, Japan) was performed twice in 2 days. His consciousness improved considerably after the first session of dialysis (E3, V4, and M6) and was completely restored on the next morning after the second session (E4, V5, and M6). The trough levels of ganciclovir in the serum and CSF were retrospectively measured and are shown in table 1.

Discussion

We describe a patient with severe ganciclovir encephalopathy. Generally, ganciclovir is well tolerated, but caution is required in patients with renal impairment. Additionally, the

severe symptoms in our patient may have been attributed to high doses of ganciclovir or valganciclovir for treatment of severe CMV enteritis.

The mechanism underlying ganciclovir encephalopathy remains largely unknown. Ganciclovir passes the blood-brain barrier [4]. Although the trough blood ganciclovir concentration in our patient was the highest reported to date, his CSF ganciclovir concentration was the second highest among the 4 patients reported to date in the literature. Such discrepancies between the CSF data and blood data may be explained by other factors, including penetration rates (how much ganciclovir passes through the blood-brain barrier), which are reported to vary among individuals [4]. However, CSF concentrations may not necessarily reflect the severity of encephalopathy. As an extreme example, 1 previous patient with an undetectable level of ganciclovir in the CSF (patient 2 in table 1) still had disturbed consciousness [1]. We speculate that the severe symptoms in our patient might have been attributed to peripheral nervous system involvement, which may be more sensitive to blood ganciclovir concentrations. Although definitive conclusions must await further studies, blood trough concentrations of ganciclovir may be more closely related to symptom severity than CSF concentrations.

Our findings show that dialysis was an effective treatment. Only withdrawal of the drug may lead to the complete resolution of symptoms. However, a fall, as observed in our patient, can cause devastating complications, an extended hospital stay, or both. In such patients, dialysis is a safe and effective treatment option. Dialysis also has a positive effect on the function of the transplanted kidney.

In summary, our experience suggests that therapeutic dialysis is a safe and effective treatment for encephalopathy as well as for a damaged transplanted kidney. The measurement of ganciclovir concentrations in the CSF may not be feasible for the management of encephalopathy in individual patients because it is not routinely performed, and because several days to several weeks are required for the results. Nonetheless, measurement of ganciclovir concentrations can play an important role in confirming the diagnosis and evaluating disease severity. We believe that accumulated knowledge on such patients with confirmed encephalopathy will lead to prompter and more accurate diagnoses.

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DOI: 10.1159/000355638

Table 1. Ganciclovir-induced encephalopathy

Patient, n	1	2	3	4
Age, years	55	n.d.	73	13
Sex	M	M	M	M
Basal disease	DM, CRF	CRF	CRF	ALL
Transplantation	Kidney	Kidney	–	Hematopoietic stem cell
CMV infection	Enteritis	Hepatitis, duodenitis	– (Hepatitis B)*	Retinitis, interstitial pneumonia
Trough ganciclovir in blood, μg/ml (after the last dose)	7.001 (48 h) 0.215 (after dialysis)	2.0 (12 h)	1.2 (72 h)	3.85 (48 h) 1.97 (72 h)
Trough ganciclovir in CSF, μg/ml (after the last dose)	2.449 (33 h)	0 (12 h)	0.75 (72 h)	2.6 (48 h)
Ganciclovir (G) oral ganciclovir (V) dose	G 150 mg × 11 days + V 450 mg × 8 days	G 10 mg/kg × 8 days	G 1.25 mg/kg × 5 days	G × 14 days + V 225 mg × ~14 days
Symptoms				
Unsteady gait	+	–	–	n.d.
Dysarthria	+	–	+ (aphasic)	n.d.
Disturbed consciousness	+	+	+	+
Other	Falls			Visual hallucination
Creatinine clearance, ml/min	24.2	n.d. (serum creatinine = 1.3 mg/dl)	n.d.	20
CSF				
White cells (/μl)	0.33	n.d.	0	n.d.
Protein, mg/dl	54	n.d.	Normal	n.d.
EEG	Slow waves	Normal	n.d.	Slow
Imaging of brain	Normal MRI	Normal CT	Left occipital, right cerebellar ischemia on CT**	n.d.
Withdrawal or decrease of ganciclovir (days needed for recovery)	Withdrawal (no recovery after 2 days)	Decreased to half dose (3)	Withdrawal (5)	Withdrawal (2)
Specific treatment (days needed for recovery)	Hemodialysis (2)	–	***	–
References	Present work	[1]	[2]	[3]

* Ganciclovir was reported to be used for hepatitis B; ** found before encephalopathy and unchanged after encephalopathy; *** the patient received regularly performed hemodialysis 3 times a week. DM = Diabetes mellitus; CRF = chronic renal failure; ALL = acute lymphoblastic leukemia; n.d. = not described.