【 CASE REPORT 】

Valacyclovir-induced Neurotoxicity in a Patient with a Preserved Renal Function

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Abstract:

Valacyclovir, a prodrug of acyclovir, is the first-line treatment for herpes zoster, but the renal function must be monitored, because acyclovir is metabolized by the kidneys. We herein report a case of valacyclovir-induced neurotoxicity with no preceding renal impairment. An 88-year-old man was admitted because of an impaired consciousness after the administration of valacyclovir at 3,000 mg daily for herpes zoster on the chest. His consciousness level gradually improved with hydration and valacyclovir withdrawal. It was later confirmed that the level of acyclovir on admission had been 35.45 µg/mL in the blood and 36.45 µg/mL in the cerebrospinal fluid.

Key words: herpes zoster, neurotoxicity, renal impairment, valacyclovir

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Introduction

Herpes zoster, reactivation of the latent varicella-zoster virus in ganglia, can spread to the neural tissue and the corresponding cutaneous dermatome (1). Antiviral drugs inhibiting the replication of herpes zoster by triphosphates, such as acyclovir and its prodrug valacyclovir, have been established as the first-line treatment for this condition (1) with an excellent safety profile (2, 3). However, attention should be paid to drug-induced neurotoxicity in patients with renal impairment, as these agents are metabolized by the kidneys (4).

We herein report a case of herpes zoster in which valacyclovir-induced neurotoxicity developed in the setting of no preceding renal impairment.

Case Report

An 88-year-old man was admitted to our hospital because of an impaired consciousness. The patient had been in his normal state of health until six days before admission, when painful skin blisters developed on the right side of the chest. A diagnosis of herpes zoster was made, and valacyclovir at

3,000 mg daily with levofloxacin at 500 mg daily was prescribed by his physician. Laboratory tests performed 2 weeks before admission indicated a normal renal function with a creatinine level of 0.43 mg/dL and urea nitrogen level of 17.1 mg/dL (Table). One day before admission, his consciousness level was slightly decreased, and intravenous hydration was initiated with little improvement. The next day, the patient was referred to another hospital because the level of consciousness had deteriorated. Computed tomography of the brain and abdomen obtained without the administration of contrast material reportedly was unremarkable. He was then transferred to the emergency department of our hospital for further examination.

The patient had a history of asthma, dyslipidemia, heart failure, overactive bladder, hypertension, diabetes mellitus, reflux esophagitis, benign prostate hypertrophy, and pancreatitis. His medications included ipragliflozin at 50 mg, omeprazole at 10 mg, metformin at 500 mg, amlodipine at 5 mg, imidapril at 5 mg, glimepiride at 0.5 mg, tamsulosin at 0.2 mg, and imidafenacin at 0.1 mg. The last administration of valacyclovir was 32 hours before admission, and that of levofloxacin was 48 hours before admission. He did not smoke or drink and had no known allergies. His family history was unclear because he had lived alone for decades

Table.   Laboratory Data.

Variable	Reference range	Two weeks before admission	On admission	Six days after admission
White blood cell count (/μL)	4,000-9,000	14,000	8,500	12,000
Hemoglobin (g/dL)	11.5-16.5	13.4	11.3	12.3
Platelet count (/μL)	150,000-420,000	292,000	177,000	117,000
Total bilirubin (mg/dL)	≤1.2		0.2	0.4
Aspartate aminotransferase (U/L)	≤30	17	48	24
Alanine aminotransferase (U/L)	≤30	13	36	31
Lactate dehydrogenase (U/L)	110-120	281	353	287
Total protein (g/dL)	6.7-8.8		4.5	4.3
Albumin (g/dL)	≥4.0	3.5	2.3	2.3
Sodium (mEq/L)	135-147	148	151	159
Potassium (mEq/L)	3.6-5.0	4.3	3.0	2.9
Chloride (mEq/L)	100-110	107	110	120
Urea nitrogen (mg/dL)	8-20	17.1	68	47
Creatinine (mg/dL)	0.45-0.81	0.43	1.60	0.91
Amylase (U/L)	37-125		299	36
Creatine kinase (U/L)	≤175		414	31
C-reactive protein (mg/dL)	≤0.25		5.00	2.36
Blood sugar (mg/dL)	70-108	288	222	165
Low-density lipoprotein cholesterol (mg/dL)	70-139	78		
Triglyceride (mg/dL)	35-148	94		
Glycated hemoglobin (%)	4.6-6.2		8.1	
eGFR (mL/min/1.73 m^2)	≥60	135.1	32.1	59.5

eGFR: estimated glomerular filtration rate

with little contact with his relatives.

On an examination, he was not lethargic but was drowsy and disoriented (Japan Coma Scale 3). The blood pressure was 91/63 mmHg, the pulse was 50 beats per minute, the respiratory rate was 14 breaths per minute, and the oxygen saturation was 96% while breathing ambient air. The body surface temperature was below the lower limit of the measurable range; the rectal temperature was not measured at the emergency department. His capillary blood glucose level was 224 mg/dL. Manual muscle testing was not performed, but he continued to move his upper extremities. There was no muscle fasciculation, increased or decreased muscle tonus, sensory impairment, or tendon reflex abnormalities.

The findings of arterial blood gases, assessed with a supplemental oxygen flow at 1 liter per minute via nasal cannula, were a partial oxygen pressure of 130.0 mmHg, partial carbon dioxide of 56.3 mmHg, lactate of 9 mg/dL, bicarbonate of 30.2 mmol/L, and pH of 7.349. The C-reactive protein level was 5.00 mg/dL, the urea nitrogen level was 68 mg/dL, and the creatinine level was 1.60 mg/dL. The other results are shown in the Table. His cerebrospinal fluid was clear with a first pressure of 105 mm of water, last pressure of 50 mm of water, protein level of 85 mg/dL, glucose level of 151 mg/dL, and cell count of 1 per cubic millimeter. Electrocardiography demonstrated sinus bradycardia with a heart rate of 40 beats per minute and prominent J waves (Figure). The chest radiograph findings were normal.

A tentative diagnosis of valacyclovir-induced neurotoxic-ity was made, and hydration was intravenously initiated, along with valacyclovir withdrawal and passive warming with blankets. Echocardiography revealed a left ventricular ejection fraction of 44%, normal chamber sizes, and mild mitral and tricuspid valve regurgitation. Blood cultures were obtained and later found to be sterile. His body surface temperature returned to 36.4°C at 12 hours after admission, accompanied by the disappearance of the prominent J waves when the blood pressure and heart rate were 94/44 mmHg and 74 beats per minute, respectively. The fractional excretion of urea, assessed 3 days after admission, was 28.8% (reference 50-65%, with the value ≤35% indicating prerenal acute kidney injury) [5]. The cerebrospinal fluid was confirmed to be negative for herpes simplex virus, cytomegalovirus, and varicella zoster virus. His consciousness level and laboratory tests, as shown in Table, gradually improved within a week after admission, although the subsequent clinical course was complicated with liver enzyme elevation and pressure ulcers, which were treated conservatively. It was later confirmed that the levels of acyclovir were 35.45 μg/mL in the blood (therapeutic reference ranges, 0.4 to 2.0) [6, 7] and 36.45 μg/mL in the cerebrospinal fluid on admission, and 0.63 μg/mL in the blood 6 days after admission.

The patient was scheduled to be transferred to a rehabilitation hospital, but approximately one month after admission, hemodynamic collapse suddenly occurred. Resuscitation was performed without success, and no autopsy was
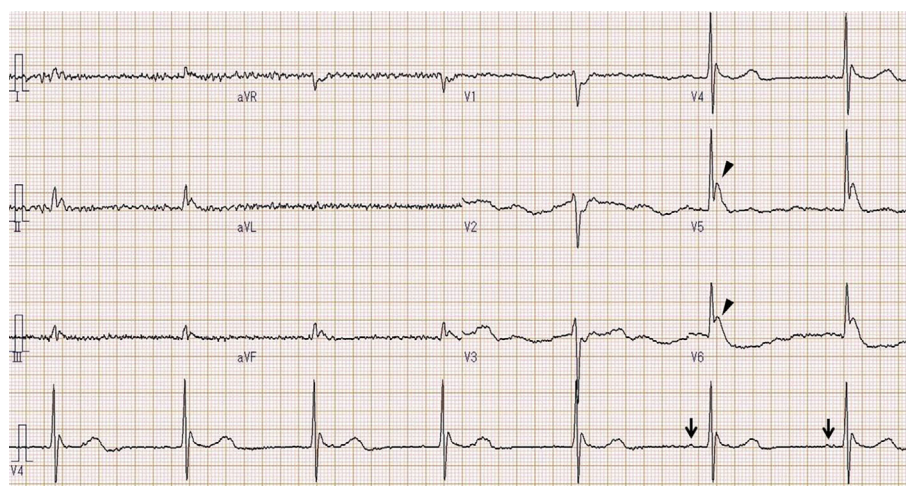
Figure. Electrocardiogram findings on admission. Faint P waves in lead V₄ (arrows) indicate sinus bradycardia. Neither prolonged QT intervals nor ST-segment changes are obvious, but prominent J waves are noted (arrowheads).

performed.

Discussion

Our patient likely developed neurotoxicity due to valacyclovir; however, the possibility of acute encephalitis due to herpes zoster or other organisms cannot be completely ruled out. Acute encephalitis is a rare but serious complication of herpes zoster infection, and this unusual condition is generally accompanied by disseminated skin lesions and pleocytosis in the cerebrospinal fluid (1, 8), none of which were observed in the present case. Acute encephalitis associated with herpes zoster usually occurs around a week after the onset of skin eruption, whereas drug-induced neurotoxicity develops within three days after the administration of antiviral drugs (9, 10). The direct effects of valacyclovir on the brain remain unclear, but high concentrations of valacyclovir may inhibit deoxyribonucleic acid polymerase, resulting in alteration of the mitochondrial function (6, 11).

Drugs other than valacyclovir were also considered as causes of the impaired consciousness in the present case. In particular, concerns persist regarding the neurotoxic effects of levofloxacin, a third-generation fluorinated quinolone antibiotic, because of its predominantly renal excretion (12) and simultaneous administration with valacyclovir. Neurotoxic manifestations related to quinolones include headache, dizziness, seizures, delirium, and confusion (13). The diversity of symptoms may be explained by variability in the binding potency of quinolones to gamma-aminobutyric acid receptors (14), which is considered to be one mechanism underlying quinolone-induced neurotoxicity (15). Although the concentration of levofloxacin was not measured in the present case, we consider levofloxacin-induced neurotoxicity to be less likely due to the half-life of levofloxacin (i.e., 4 to 7 hours in healthy volunteers (16) and 34.5 hours in patients who needed extended daily dialysis (17). The present case was transferred to our hospital 48 hours after the cessation of levofloxacin. His renal function was not severely impaired on admission and improved afterwards, but consciousness recovery was delayed.

It has become increasingly recognized that renal impairment is a risk factor of acyclovir neurotoxicity because acyclovir, which is the active drug of valacyclovir, is excreted by the kidneys via tubular secretion and glomerular filtration, although valacyclovir itself is eliminated in the feces (4, 6, 18). Dose adjustment of valacyclovir should be considered in patients with renal impairment, e.g. creatinine clearance <50 mL/min (1). The half-life of acyclovir is approximately 3 hours in healthy volunteers, whereas it can be extended up to 14 hours in patients with end-stage renal disease (6, 19). The mechanism underlying the new onset of renal impairment in the present case remains unclear, but a gradual loss of appetite due to the herpes zoster infection may have led to dehydration and renal impairment. This speculation was consistent with the decreased fractional excretion of urea (5). Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, may have exacerbated the dehydration in the present case.

Another explanation for the transient renal impairment is the direct toxic effects of valacyclovir on the renal function, although the risk of valacyclovir-induced renal impairment is likely low (20). Drug interaction with valacyclovir has been reported, such as for antacids like cimetidine, probenecid, digoxin, and thiazide diuretics (21), but none of these had been prescribed in the present case. As the bioavailability of valacyclovir is three to four times higher than that of acyclovir (19, 22), individual vulnerability and frailty should be carefully considered in order to avoid valacyclovir-induced neurotoxicity. This condition is likely to occur among elderly patients not only because they are prone to dehydration but also because the severity and incidence of herpes zoster increases with age (1, 23). Drug-induced neurotoxicity is generally resolved within two to seven days after the cessation of antiviral drugs, along with supportive care, and

hemodialysis may be considered in severe cases because acyclovir has a low volume distribution and low protein binding (6). In such high-risk patients, a potent helicase-primase inhibitor, amenamevir, which was recently approved for the treatment of herpes zoster, may be considered as an alternative to acyclovir and valacyclovir, as this novel class of antiviral agents seems to require no dose adjustment for renal impairment (24, 25). It is important to note that we cannot completely rule out the possibility of other drugs, such as levofloxacin, as the cause of the transient renal impairment.

This case highlights the importance of closely monitoring herpes zoster patients treated with antiviral agents, particularly vulnerable and frail elderly patients, even in the absence of preceding renal impairment.

The authors state that they have no Conflict of Interest (COI).

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