Valacyclovir-Associated Neurotoxicity in a Patient With Kidney Failure

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Valacyclovir, a prodrug of acyclovir, is a widely prescribed medication for treating varicella-zoster virus (VZV, shingles) owing to its greater bioavailability and lower frequency of administration.[1] Once in the cells, valacyclovir is rapidly converted to the active drug, acyclovir monophosphate, and the amino acid valine via hepatic first-pass metabolism.[2] Acyclovir monophosphate then inhibits herpes DNA polymerase, terminating viral replication. It has a very strong antiviral activity against herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) and against VZV.[3]

Valacyclovir is generally well-tolerated; however, several reports of neurotoxicity have been described in patients with and without underlying renal impairment. Despite these reports, valacyclovir-induced neurotoxicity can be easily missed because the patient is encephalopathic. Also, most hospital laboratories do not measure levels of valacyclovir in routine urine toxicology screens. In such circumstances, the diagnosis of possible valacyclovir toxicity depends on the investigative skills of the clinician.

The likelihood of drug toxicity in the settings of acute or chronic kidney disease (CKD) is always high. Thus, in any patient with CKD presenting with acute encephalopathy without obvious signs and symptoms of an infection, drug-induced toxicity should be high on the differential diagnosis, since prompt recognition and treatment can be life-saving. We report a case in which swift recognition of valacyclovir-induced neurotoxicity in a patient with kidney failure on dialysis led to prompt targeted management, sparing extensive investigations that would have been costly and unhelpful.

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CASE REPORT

A 77-year-old woman with kidney failure on hemodialysis and with dementia was brought to our emergency department with acute-onset confusion. The patient's daughter reported that the woman had been doing relatively fine 2 days before presentation. The patient had been prescribed valacyclovir, 1000 mg, to be taken every 8 hours, for a diagnosis of shingles made by her primary care physician. The daughter noted that the patient had become more drowsy, restless, lethargic, and dysarthric, and had begun to exhibit signs of confusion after 2 doses of valacyclovir. The patient was also noted to have had visual hallucinations prior to presentation. The patient had not experienced similar episodes of such symptoms in the past.

On presentation, the patient was noted to have a blood pressure of 165/70 mm Hg, a pulse rate of 88 beats/min, a respiratory rate of 16 breaths/min, and an oxygen saturation of 97% on room air. Physical examination revealed a noncommunicative patient with upper- and lower-extremity tremors at rest and with motion. A blistering rash with crusting was noted on the left axillary area, T4 dermatome. Lung and heart examination findings were unremarkable.

Results of a complete blood count and a complete metabolic panel, as well as the magnesium level, phosphorus level, urinalysis findings, acetaminophen and salicylate levels, and urine toxicology screen results were unremarkable (**Table 1**).

Computed tomography scans of the brain without contrast did not show any acute intracranial findings. Valacyclovir toxicity was thus suspected, and the patient was scheduled for emergent dialysis, of which she had daily sessions for 4 consecutive days. A notable change in her status became obvious after 2 consecutive dialysis sessions; her tremors markedly decreased, and improvement in her mentation became evident.

She was discharged on day 5 of hospitalization after complete resolution of her symptoms and was noted to be at her baseline condition as confirmed by her daughter at the bedside.

DISCUSSION

According to the Centers for Disease Control and Prevention, approximately 30% of persons in the United States will be infected with herpes zoster during their lifetime.[4] The prevalence and incidence rates of herpes is known to increase with age. Valacyclovir is the drug of choice because of better medication

Table 1. Pertinent Laboratory Data at the Time of Presentation

Analyte	Value at Admission	Reference Range
White blood cells ($\times 10^3/\mu L$)	7.3	4.5-11.0
Red blood cells ($\times 10^6/\mu L$)	3.78	3.8-5.2
Hemoglobin (g/dL)	11.6	12.0-15.0
Platelet count ($\times 10^3/\mu L$)	183	150-450
Sodium (mEq/L)	137	136-145
Potassium (mEq/L)	4.4	3.5-5.1
Magnesium (mg/dL)	2.1	1.8-2.4
Phosphorus (mg/dL)	3.2	2.5-4.9
Urea nitrogen (mg/dL)	25	7-18
Creatinine (mg/dL)	4.72	0.60-1.30
Estimated glomerular filtration rate (mL/min)	9	≥75
Aspartate aminotransferase (U/L)	14	15-37
Alanine aminotransferase (U/L)	12	12-78
Alkaline phosphatase (U/L)	103	46-116
Ammonia (µmol/L)	17	11-32

Table 2. Suggested Valacyclovir Dose Adjustments Based on Renal Function

Creatinine Clearance	Dosing (Oral)
<10 mL/min	500 mg every 24 h
10-29 mL/min	1 g every 24 h
30-49 mL/min	1 g every 12 h
>50 mL/min	1 g every 8 h

adherence (prescribed as a 3 times a day regimen, rather than the 5 times a day regimen of acyclovir). The half-life of acyclovir in healthy subjects is approximately 2.5 to 3.3 hours, whereas in patients with kidney failure, it can be up to 14 hours.[1,5]

The symptoms associated with valacyclovir-induced neurotoxicity typically begin within 1 to 3 days of starting the medication.[6] Disturbances in the level of consciousness and confusion are the most frequently reported symptoms, followed by disturbances of perception, including hallucinations.[3] Less commonly, neurotoxicity may manifest as ataxia, dysarthria, myoclonus, or rhabdomyolysis and in the most severe cases as seizures, coma, and death.[3,7] Depending on the degree of renal impairment and frequency of hemodialysis, symptoms usually resolve within a week of discontinuation of the medication.[6] Therefore, it is of prime importance for physicians to recognize the common and less-common presentations of neurotoxicity.

When treatment with valacyclovir is indicated, appropriate dosing must be adjusted based on creatinine clearance (**Table 2**), and specific guidelines on timing of administration based on the dialysis schedule must be followed. Our patient was prescribed a dose of 1 g every 8 hours, which was significantly higher than her recommended dose based on creatinine clearance. This most likely led to neurotoxicity and should serve as a caution to primary care providers who are certain to treat shingles in the future.

When valacyclovir neurotoxicity is suspected, the drug should be withheld, followed promptly by hemodialysis, which removes 40% to 50% of the drug in a 4-hour session.[2,7] If a patient's mental status does not improve in 2 to 3 days despite these measures, other etiologies must be considered.[8] The rapid resolution of our patient's symptoms after valacyclovir discontinuation and dialysis supports a causal effect.

In conclusion, when prescribing valacyclovir, especially in elderly patients, dose adjustment must be made based on renal function, and extra considerations must be made for patients on dialysis. For prompt recognition of symptoms of toxicity, patient and caregiver education must also be provided at the time of drug prescription. In the event of neurotoxicity, performing a good history and physical examination are invaluable to directed management, saving time and cost that would be otherwise wasted in the pursuit of other etiologies. ■

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