Case Files of the Harvard Medical Toxicology Fellowship: Valacyclovir Neurotoxicity and Unintentional Overdose

Colin Huguenel · Diana Felton · Rebecca Bruccoleri ·
Steven Salhanick

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Case Presentation

A 24-year-old female with idiopathic end-stage renal disease (ESRD) for the past 8 months, currently on home peritoneal dialysis, presented to an outside hospital with progressive confusion, tremulousness, clumsiness and a sensation of being “outside her own body.” The patient had been in her usual state of health until 2 days prior, around the time she concomitantly began to have a breakout of her genital herpes. The patient was previously prescribed valacyclovir, dosed at 1000 mg twice daily $\times$ 3 days, to be taken during outbreaks. This was the first outbreak of her genital herpes since the development of her renal disease. Since starting the valacyclovir, her neurologic symptoms had gradually worsened, to the point that on the evening prior to admission, she was too confused to even complete her scheduled peritoneal dialysis. She was seen that night at an outside hospital (OSH A) where she regularly receives her care. There, she was noted to be hypertensive but otherwise had a reassuring exam. She was given labetalol orally and instructed to follow up closely with her primary care practitioner. Due to her worsening symptoms, the patient’s family called EMS the following morning, with a plan to bring the patient to OSH A.

C. Huguenel · D. Felton · R. Bruccoleri · S. Salhanick
Harvard Medical Toxicology Program, Department of Emergency
Medicine, Beth Israel Deaconess Medical Center, W-CC2, 1
Deaconess Road, Boston, MA 02115, USA

D. Felton (✉) · R. Bruccoleri · S. Salhanick
Massachusetts and Rhode Island Center for Poison Control and
Prevention, Boston Children’s Hospital, 300 Longwood Avenue,
Mailstop 3025, Boston, MA 02115, USA
e-mail: diana.felton@childrens.harvard.edu

Unfortunately, en route to that hospital, the patient experienced a tonic-clonic seizure. EMS, therefore, diverted to a different hospital (OSH B), where she was found to be in status epilepticus resistant to both lorazepam and phenytoin. The patient was subsequently intubated with rapid sequence induction and further sedated with propofol, which terminated her seizure activity. Initial labs performed at OSH B showed a creatinine of 17 mg/dL (1503 μ mol/L) although otherwise normal electrolytes, a negative urine and serum toxicology screen, a lumbar puncture with normal results, and a non-contrast head CT which was negative for acute bleed.

What is the Pharmacology and Use of Valacyclovir?

Valacyclovir (Fig. 1) is a L-valyl ester prodrug of acyclovir (Fig. 2), which has a markedly greater bioavailability than acyclovir itself (about 55 % vs. 15 %) [1]. It is rapidly converted to the active drug acyclovir as well as the amino acid valine via hepatic first-pass metabolism [2].

Subsequent pharmacology follows that of acyclovir. Acyclovir is a synthetic purine nucleoside analog, which is converted into a monophosphate form by viral thymidine kinase, which selectively outcompetes cellular thymidine kinase (about 3000 times greater affinity) for the phosphorylation of acyclovir. The monophosphate form is further phosphorylated into the active triphosphate form, acyclo-GTP, by host cellular kinases. This final acyclo-GTP is a potent competitive inhibitor of viral DNA polymerase, and similar to its pathway during metabolism, viral polymerase has approximately 100 times greater affinity for acyclo-GTP compared to cellular polymerase. The monophosphate form can also be incorporated into viral DNA, resulting in chain termination [1].

The prodrug valacyclovir is fecally excreted, whereas the active drug, acyclovir, is eliminated by the kidneys via tubular secretion and glomerular filtration. This makes it especially susceptible to alterations in renal function [1, 3]. The half life

Fig. 1 Valacyclovir

of acyclovir in healthy volunteers is measured at 2.5–3.3 h, whereas in patients with ESRD, it can be up to 14 h [1, 4].

Valacyclovir, and more specifically, its metabolite acyclovir, is active against most species in the herpes virus family, including herpes simplex virus type I and II (HSV-1 and 2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), although it is predominantly active against HSV and to a lesser extent against VZV. Its efficacy against EBV and CMV is limited, and it is inactive against latent viruses in nerve ganglia. Valacyclovir is preferred to acyclovir for multiple reasons. In addition to its higher bioavailability, valacyclovir can be dosed twice a day as opposed to the laborious five times a day required for acyclovir. Valacyclovir has been shown to be as efficacious as acyclovir in treating both genital herpes and herpes zoster [1, 5].

Is Unintentional Overdose of Valacyclovir a Common Occurrence?

Intentional ingestions of valacyclovir are quite rarely reported. Overdoses of up to 20 g have been associated with the

development of neurotoxicity [6]. More commonly, although still rare, cases of valacyclovir neurotoxicity occur in the setting of chronic or acute renal failure [3, 7], although cases without preceding renal failure have also been described [5, 6].

A case series from Japan demonstrated that all patients who exhibited valacyclovir neurotoxicity had either preceding acute or chronic renal failure, with a vast majority (85 %) of patients having chronic renal failure or requiring dialysis. In those patients where acute kidney injury was the precipitant for developing neurotoxicity, it was felt that acyclovir itself was the etiology of their kidney injury. Additionally, the majority of patients within this series had received excessive doses of valacyclovir given their existing renal dysfunction [3].

A specific case within this series describes a 73-year-old woman suffering from Alzheimer's dementia who was prescribed valacyclovir for herpes zoster of the trigeminal nerve. She developed a gradual loss of appetite, followed by difficulty swallowing within 5 days of starting treatment. Her mental status further declined to the point where she no longer exhibited volitional movement. Work up demonstrated acute kidney injury on top of chronic renal failure. Her valacyclovir was discontinued, and within 24 h, she had regained spontaneous movement and speech, and baseline level of consciousness was restored within 2 weeks [3].

A separate case from Japan detailed a 67-year-old man, on peritoneal dialysis for 2 years, started on valacyclovir for herpes zoster of the right femoral region. Within 5 days, he began to have florid hallucinations. He was admitted to the hospital and maintained on his usual peritoneal dialysis schedule. Within 7 days, his serum acyclovir level had fallen to one-thirtieth of its initial value [8].

A third case from France describes a 60-year-old woman on peritoneal dialysis who was started on valacyclovir for thoracic dermatomal herpes zoster eruption. On the third day of therapy, she became disoriented with visual and auditory hallucinations as well as delirium. After dose adjustment of valacyclovir, the patient recovered normal cognitive function and her hallucinations ceased within 3 days [4].

How does Valacyclovir Toxicity Manifest?

Because of its rapid metabolism to acyclovir, there is very little specific human data on valacyclovir toxicity. Instead, cases and studies of toxicity from these medications are generally grouped together in the medical literature. Most patients with valacyclovir or acyclovir ingestion or unintentional overdose experience only mild or moderate effects, including nausea, vomiting, and headache. The toxidrome of valacyclovir neurotoxicity was first reported by Linssen-Schuurmans et al. in 1998 [7], and a subsequent 20 cases of neurotoxicity were assembled by Asahi et al. in 2009 [3].

Fig. 2 Acyclovir

Neurotoxicity usually manifests within the first 24 to 72 h of therapy and can resolve completely within 2 to 7 days after cessation of treatment, depending on renal function of the patient, and utilization of dialysis [9]. Neurotoxicity consists of a diverse array of symptoms. Early manifestations may include lethargy, confusion, and ataxia [10]. Patients and their families describe a noticeable decrease in motor function or clumsiness. In more severe cases, patients can develop hallucinations, dysarthria, myoclonus, fasciculations with subsequent rhabdomyolysis, seizures, and ultimately coma or death [3, 10, 11]. Acute renal failure can occur from acute precipitation of acyclovir crystals within renal tubules and subsequent obstructive nephropathy [1, 12]; however, it has been shown that acyclovir can also cause acute interstitial nephritis [13]. As such, acyclovir and therefore valacyclovir as well, can induce the acute kidney injury responsible for their own neurotoxicity.

Does this Patient have Acyclovir Neurotoxicity?

Our patient presents with neuropsychiatric symptoms including confusion, tremulousness, ataxia, decreased motor coordination, and what sounds to be hallucinations (being outside her own body), followed progressively by a decline in overall mental status and seizures. All of these fit clinically with a diagnosis of acyclovir neurotoxicity. Also supporting this diagnosis is that the patient has ESRD. As discussed, this is a major predisposing factor for the development of neurotoxicity. Furthermore, her report of taking valacyclovir 1000 mg twice daily, with a history of ESRD and a creatinine of 17 mg/dL at OSH B clearly demonstrates that this patient is taking a functional overdose of this medication, making neurotoxicity an appealing diagnosis.

What is the Pharmacologic Basis for Symptoms Seen with Neurotoxicity?

The exact mechanism of neurotoxicity from valacyclovir and acyclovir has not been fully elucidated. One proposed mechanism is that large doses may inhibit mitochondrial DNA polymerase and alter the function of mitochondria themselves. This ability has been described elsewhere with antiviral nucleoside analogs, and it is suspected that acyclic antivirals like acyclovir may function similarly [14].

What Diagnostic Studies Exist to Confirm Acyclovir Toxicity?

The diagnosis of valacyclovir and acyclovir neurotoxicity is made largely on clinical grounds with a detailed history and examination. An index of suspicion must be raised for any patient on either of these agents who has pre-existing renal disease or has newly diagnosed kidney injury.

Acyclovir levels can be obtained from the blood, serum, CSF, or urine via liquid chromatography and tandem mass spectrometry at specialty reference laboratories [15]. However, studies have yet to show a direct correlation between symptoms and acyclovir levels in the serum or CSF [16]. Elevated CSF levels of 9-carboxymethoxymethylguanine (CMMG), a metabolite of acyclovir, have been reported in patients with valacyclovir and acyclovir neurotoxicity. Interestingly, all subjects in this study who were treated with acyclovir and valacyclovir but whom were asymptomatic had undetectable CMMG levels, suggesting that CMMG may play a role in the neuropsychiatric toxic effects [17].

Case Continuation

The patient was transferred to our tertiary care facility for further management. On arrival, she was hemodynamically stable, intubated, and sedated with propofol. Physical examination demonstrated withdrawal to noxious stimuli, pupils that were 2 mm, nonreactive, and without blink to threat. Corneal and gag reflexes were intact. There was neither hyperreflexia nor clonus in the extremities. The patient remained with low urine output but she was not anuric. Repeat labs again showed severe renal failure with BUN 69 mg/dL (24.6 mmol/L) and creatinine 17.6 mg/dL (1556 μ mol/L), but with otherwise normal electrolytes. CBC was unremarkable. Repeat urine and serum toxicology screens were negative. A 24-h EEG was obtained, which did not show any evidence of seizure activity, and the patient was maintained on 3 days of phenytoin for seizure prophylaxis. She was extubated on the third day; however, her blood pressure acutely increased to 190/130 mmHg, and she was treated with multiple doses of enalapril, labetalol IV, and a hydralazine drip. CT angiographic imaging of the abdomen and pelvis did not demonstrate any evidence of renal artery stenosis. Plasma and urinary metanephrines were normal. An MRI of the brain demonstrated a subtle abnormality within the parietal lobes bilaterally, which suggested the possibility of posterior reversible leukoencephalopathy.

What Other Conditions Should be Included in the Differential Diagnosis for Acyclovir Neurotoxicity?

The differential diagnosis for patients exhibiting acyclovir neurotoxicity includes meningitis, primary psychiatric disorders, HSV encephalitis, herpes zoster associated encephalitis (HZAE), and cerebral vascular disease. Distinguishing between acyclovir neurotoxicity and herpes viral encephalitis (either simplex or zoster) is crucial, as patients who are on valacyclovir or acyclovir for herpes viral outbreaks are obviously at risk for both pathologies. Acyclovir neurotoxicity

usually occurs within the first 72 h of therapy, whereas the average time between onset of dermatologic and neurologic symptoms in HZAE is around 7 days [18, 19]. Clues such as headache, fevers, and cranial neuropathies in the patient's preceding clinical history are also suggestive of an infectious cause, although admittedly, they are only present in a minority of cases of HZAE [20]. In an acute setting, without the benefit of antecedent history, acyclovir neurotoxicity and herpes viral encephalitis may be clinically indistinguishable, sharing an alteration of mental status as their most prominent and frequent manifestation. As such, CSF analysis is often necessary in these patients, as the delineation between the two entities is crucial. Treating empirically for a misdiagnosis of encephalitis would only serve to worsen the symptoms caused by valacyclovir or acyclovir toxicity.

Other toxic ingestions may be included in the differential for acyclovir neurotoxicity. Myoclonus can be seen in cases of gabapentin toxicity, particularly with renal insufficiency, and the ataxia exhibited in acyclovir toxicity may be confused with lithium toxicity. Both of these agents could also manifest the depressed and altered mental status seen in acyclovir neurotoxicity.

How Should Acyclovir Neurotoxicity be Treated?

In cases of mild to moderate toxicity, patients generally do well with supportive care alone. Nausea and vomiting may be treated with antiemetics. In more severe overdoses, renal toxicity may possibly be mitigated with aggressive intravenous fluid hydration and close monitoring of renal function.

In patients manifesting severe toxicity, discontinuation of valacyclovir or acyclovir and supportive care remain the mainstays of therapy. Symptoms of neurotoxicity may be mitigated with administration of benzodiazepines, and consideration of airway management should occur early in patients with profound CNS depression or recurrent seizures. Similarly, seizures should be treated with benzodiazepines as first-line therapy, followed by barbiturates, and propofol should seizures persist. In general, activated charcoal may be considered in patients presenting immediately after a large intentional ingestion if they are awake, alert, and willing to drink the charcoal. As with other medications, a careful risk-benefit analysis must be undertaken prior to administration of activated charcoal to assess if the potential benefit outweighs the potential risk of aspiration.

Acyclovir has low protein binding and a low volume of distribution, and as such, its elimination may be enhanced with hemodialysis (HD). Prior reports describe removal of 30–60 % of the drug during 4-h HD sessions; however, it is rarely indicated as patients often do well with supportive care alone [2, 9, 18]. HD has been used successfully in patients with severe neurotoxicity from acyclovir and valacyclovir and should be used in these severe cases to enhance the

elimination of the offending drug [2, 3, 18]. In addition, failure to achieve substantial response to HD should prompt immediate investigation for other etiologies of the patient's symptoms, namely viral encephalitis. Standard peritoneal dialysis does not appear to be effective in enhancing the elimination of acyclovir based on the data available [3, 19], although case reports of recovery using only discontinuation of therapy and peritoneal dialysis exist in the literature [16, 18].

Case Conclusion

The patient steadily improved with continuation of her peritoneal dialysis, in conjunction with gentle IV fluid hydration. She continued to make small amounts of urine, which may have contributed some clearance of the acyclovir. She was transitioned to a regimen of carvedilol, losartan, and amlodipine orally to manage her blood pressure adequately. For seizure control, she was discharged on a regimen of levetiracetam 500 mg PO daily. Acyclovir levels were sent out and returned with an acyclovir concentration of 4.1 µg/mL, which is roughly twice the upper limit of reference ranges for peak concentration based on usual therapeutic dosing (0.4–2.0 µg/mL) [15, 21]. The acyclovir level subsequently decreased to 0.5 µg/mL 2 days later during her hospital course. She has followed up as an outpatient with both her primary care physician and with neurology, and is doing well, without any recurrence of seizures.

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Conflict of Interest Colin Huguene, Diana Felton, Rebecca Bruccoleri, and Steven Salhanick declare that they have no conflict of interest.

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