No Medicine is Benign: A Case of Valtrex Toxicity

Amelia Morgan, DO[1], Sonu Santhosh, DO[2], Raghad Hussein, MD[3]
[1]Internal Medicine-Pediatrics, Geisinger Medical Center (GMC), Danville, PA; [2]Internal Medicine, GMC, Danville, PA;
[3]Critical Care Medicine, GMC, Danville, PA

Geisinger

Introduction

Valacyclovir (Valtrex) is a routinely prescribed medication for treatment of viral infections, such as Shingles caused by varicella zoster virus (VZV). The most beneficial time to start Valtrex is within 24 hours of symptom onset with a standard dose of 1000 mg three times a day for seven days; however, specific renal dosing exists for various creatinine clearances (CrCl) (see Table 1).[8]

Creatinine Clearance (mL/min)	Valacyclovir Dosing
≥ 50	1000 mg three times per day
30-49	1000 mg two times per day
10-29	1000 mg once daily
10	500 mg once daily

Table 1. Valacyclovir dosage adjustment based on CrCl.[8]

Valtrex typically is regarded as a benign, well-tolerated medication. After ingestion, it is metabolized by the liver into its metabolite, acyclovir, which is then excreted almost exclusively in the urine (90%). Because of its pharmacokinetics, patients with chronic kidney disease (CKD), in addition to those with advanced age, can have a reduced clearing capacity of the drug. Majority of cases of toxicity are mild with symptoms of nausea, vomiting, or headaches; however, when toxic levels accumulate, symptoms can be much more severe including acute altered mental status (AMS) ranging from confusion to coma in additional to acute renal failure.[4]

Case Presentation

An 86-year-old female with past medical history significant for hypertension (HTN), CKD (Stage 3B), history of transient ischemic attack (TIA) and peripheral vascular disease (PVD) presented to an outside hospital Emergency Department after acute onset of confusion and fall at home. Initial labs were most notable for an acute creatinine (Cr) increase from baseline of 1.5 mg/dL to 3.4 mg/dL indicative of acute kidney injury. CT head (see Figure 1) completed in the ED to rule out intracranial pathology did not reveal acute abnormalities compared to previous studies. She was treated with intravenous fluids and monitored in the ED; however, she continued to remain altered prompting transfer to our tertiary care center for further work-up and evaluation. She was admitted to the medicine floor and was closely monitored.

During her initial work-up, family informed the medical team that just two days prior to presentation, she had been diagnosed with VZV infection and started on valacyclovir by her PCP.

Case Presentation Cont'd

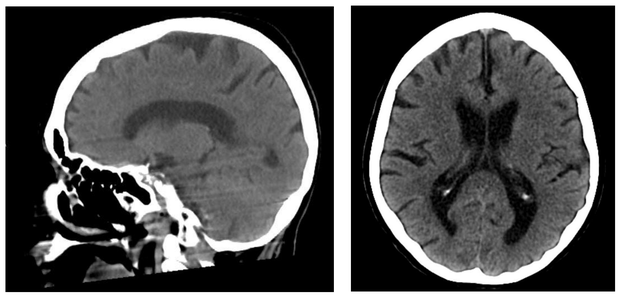

Figure 1. No acute intracranial findings, evidence of microvascular ischemic disease.

Nephrology was consulted due to the concern for possible Valacyclovir neurotoxicity as the etiology of her AMS in the setting of oliguric renal failure. A temporary hemodialysis (HD) line was placed for emergent dialysis. While being managed on the medicine floor, her mental status showed no significant improvement and respiratory status deteriorated; she was transferred to the ICU for oxygen delivery via high flow nasal cannula, followed by intubation for airway protection. Because her mental function was not recovering as anticipated, additional work-up including a lumbar puncture (LP) and an MRI brain with and without contrast (see Figure 2) were completed to investigate the etiology of her meningoencephalitis. Unfortunately, this additional testing yielded no additional information.

During this period, her renal function was stable with urine output showing some improvement (see Table 2). Her HD sessions were complicated by episodes of dramatic atrial fibrillation requiring IV rescue medications and subsequent early termination due to hemodynamic instability.

By hospital day 5, she was showing signs of meaningful recovery and was able to be extubated. Although she was not completely back to baseline, her AMS was slowly improving. She remained hospitalized on the medicine floor for an additional 7 days prior to discharge home primarily to monitor her renal function and urinary output. No additional HD sessions were needed as her Cr downtrended to 2.2 prior to discharge.

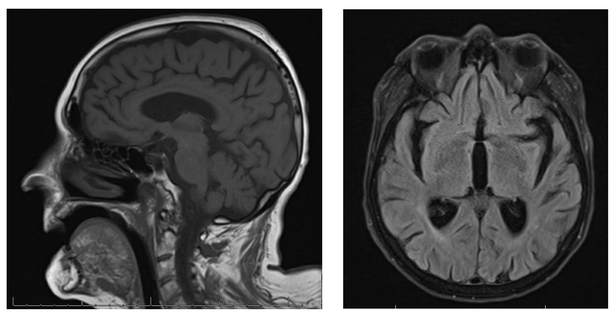

Figure 2. Moderate diffuse atrophy, dominant left intradural vertebral artery, No acute intracranial abnormalities.

Date	Creatinine (mg/dL)	BUN (mg/dL)	Urine Output (mL/day)
Admission	4.5	41	140
Day 1	5.4	49	719
Day 2	3.4	23	140
Day 3	3.5	32	138
Day 4	3.8	46	295
Day 5	2.9	50	345
Day 6	3.0	69	423
Day 7	3.1	93	332
Day 8	3.2	95	1025
Day 9	3.1	97	2080
Day 10	2.9	102	1300
Day 11	2.4	95	1300
Day 12	2.2	90	1250

Table 2. Hospital day trend of serum Cr and UOP

Results

Work-up included:

- Frequent blood work primarily to monitor Cr and BUN (see Table 2)
- Urine toxicology screen (negative)
- Lactate which was initially elevated to 4.5 at time of admission, downtrended over 3 days to 2.1
- Infectious cultures including blood, urine, and cerebrospinal (CSF) fluid which were all unremarkable
- Imaging (as seen in Figures 1 and 2) with no significant abnormalities

Discussion

Valacyclovir neurotoxicity has been discussed previously in the literature. Diagnosis is primarily one of exclusion in that other causes of AMS needed to be ruled out prior to making the diagnosis with serum Valtrex levels not correlating with presentation. Typically, symptoms start within 1-3 days of starting valacyclovir or acyclovir, as valacyclovir is metabolized into acyclovir metabolites. Caution is recommended in determining herpes zoster related encephalitis compared with neurotoxicity as it greatly changes management and would impact mortality. It was found in our patient that she had inadvertently been prescribed 2000 mg TID instead of the typical 1000 mg TID dosing which likely precipitated her acute kidney injury in addition to her AMS. A quality safety form was completed to help determine the underlying cause of this error, however for this patient it cost her a 12-day hospital stay, intubation and countless other invasive tests.

Conclusion

Despite Valacyclovir being routinely prescribed and generally well tolerated, doses of the medication should be judiciously prescribed especially in the elderly population or in those at risk of renal dysfunction. Carefully adjusting the medication based on renal function should be reviewed by clinicians and pharmacists alike to prevent adverse events.

References

1. Bonnie Bean, Dorothee Aeppli. Adverse Effects of High-Dose Intravenous Acyclovir in Ambulatory Patients with Acute Herpes Zoster. *The Journal of Infectious Diseases.* Volume 151, Issue 2, February 1985, Pages 362–365, DOI: 10.1093/infdis/151.2.362
2. Ferreira M, Vega C, Rivas B, Selgas R. Acute renal failure and severe neurotoxicity after unintentional overdose of valacyclovir in a geriatric population: A case report. *Nefrologia.* 2018 May-Jun;38(3):323-325. DOI: 10.1016/j.nefro.2017.05.007
3. G. Kambhampati, U. Pakkivenkata, and A. Kazory. Valacyclovir neurotoxicity can be effectively managed by hemodialysis. *European Journal of Neurology*, vol. 18, no. 3, p. e33, 2011.
4. C. Huguenel, *et al.* Case Files of the Harvard Medical Toxicology Fellowship: Valacyclovir Neurotoxicity and Unintentional Overdose. *J Med Toxicol*. 2015 Mar; 11(1): 132–136.
5. Kassam AS, Cunningham EA. Cotard Syndrome Resulting From Valacyclovir Toxicity. *Prim Care Companion CNS Disord*. 2018 Feb 1;20(1):17l02143. doi: 10.4088/PCC.17l02143
6. Sadjadi SA, *et al.* Acyclovir neurotoxicity in a peritoneal dialysis patient. *Am J Case Rep*, 2018; 19: 1459-1462. DOI: 10.12659/AJCR.911520
7. T. Vander, M. Medvedovsky, Y. Herishanu. Encephalopathy Induced by Oral Acyclovir in a Patient with Normal Renal Function. *Journal of Infection*, 2003, Volume 46, Issue 4, 2003, Page 286, DOI: 10.1053/jinf.2002.1119
8. Valacyclovir. IBM Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Accessed February 24, 2021. http://www.micromedexsolutions.com.
9. Yoshimura T, Kawasaki T, Shirota A, Saeki M, Okada Y, Okada H. Valacyclovir-induced Neurotoxicity in a Patient with a Preserved Renal Function. *Intern Med*. 2018 Nov 1;57(21):3213-3216. doi: 10.2169/internalmedicine.0403-17