CASE REPORT

A case of acyclovir neurotoxicity presenting with atypical cerebrospinal fluid findings

Guramrinder Singh Thind, Richard Roach

Internal Medicine, Western Michigan University School of Medicine, Kalamazoo, Michigan, USA

Correspondence to

Dr Guramrinder Singh Thind, guramrinder.thind@med.wmich.edu

Accepted 5 May 2017

SUMMARY

An 82-year-old man with a history of end-stage renal disease presented with progressively worsening confusion and somnolence for the past 4–5 days. The patient was diagnosed with herpes zoster by his primary care physician 5 days ago and was started on a course of valacyclovir 1 g three times a day (dose not adjusted for renal impairment). A lumbar puncture was performed and cerebrospinal fluid (CSF) studies revealed 37 white blood cells (WBCs)/hpf (100% monocytes), protein 64 mg/dL and glucose 52 mg/dL. He was started on ceftriaxone, ampicillin and acyclovir. MRI of the brain was done and was unremarkable. Acyclovir-induced encephalopathy was high on differential, but his CSF findings were concerning for viral encephalitis. Nonetheless, all antimicrobials were discontinued and he was scheduled for a 5-hour dialysis session. The very next day, he showed immense improvement and eventually recovered completely. CSF PCR tests for both herpes simplex virus and varicella zoster virus came back negative.

BACKGROUND

Valacyclovir is the prodrug of acyclovir, 90% of which is excreted renally.¹ Failure to adjust its dose in patients with renal disease can lead to toxicity. Acyclovir and related drugs are known to cause neurotoxicity at higher doses. This adverse effect is rare and often under-recognised by clinicians. Lack of awareness of this adverse effect can lead to mismanagement. Cerebrospinal fluid (CSF) studies are typically normal in acyclovir neurotoxicity, but can rarely be abnormal.

CASE PRESENTATION

An 82-year-old man was brought to the emergency room from a nursing home with concerns of altered mental status. He had a history of end-stage renal disease due to long-term type 2 diabetes mellitus and was on scheduled dialysis. The patient was due for dialysis on the day of admission, but he had to be brought in to the emergency room instead due to his progressively worsening mentation. He also had a history of coronary artery disease, chronic atrial fibrillation, gastro-oesophageal reflux disease and gout. Of note, the patient was seen by his primary care provider 5 days prior to presentation for a right flank rash. He was diagnosed with herpes zoster at that time and was started on valacyclovir, which he had been taking every day. The caregiver was not able to provide the details of the valacyclovir dosage at that time.

History was obtained from the caregiver. The patient reportedly had been having progressively worsening confusion and somnolence for the past 4–5 days. On the day of admission, the patient also had urinary incontinence, was non-convulsant and was not following any commands. He was afebrile on presentation and vital signs were stable. On physical examination, the patient was somnolent. He was not oriented to time, place or person. His speech was incomprehensible. There was no evidence of any focal deficits as the patient was moving all four extremities and was withdrawing to pain. Deep tendon reflexes were normal and symmetrical. Brudzinski's test was negative, and the patient did not have neck stiffness.

Initial laboratory workup was unremarkable other than evidence of renal dysfunction. His white blood cell (WBC) count was $9.6 \times 10^9/L$. CT scan of the head ruled out any acute intracranial abnormality. Chest X-ray showed a right-sided infiltrate concerning for pneumonia, and he was started on ceftriaxone and azithromycin. The patient also underwent an elective 3-hour haemodialysis session on the day after the admission. However, patient's mentation did not improve with this treatment.

INVESTIGATIONS

Eventually, a lumbar puncture was performed on the third day. CSF studies revealed 37 WBCs/mm³ (100% monocytes), protein 64 mg/dL and glucose 52 mg/dL. These findings were concerning for viral encephalitis. His antimicrobial therapy was switched to ceftriaxone, ampicillin and acyclovir 5 mg/kg every 24 hours. At this point, the infectious disease service was consulted by the primary team. The infectious disease team contacted the nursing home to obtain further information about the dose of valacyclovir that the patient had been taking. It was then learnt that the patient was prescribed 1 g three times a day of valacyclovir. Evidently, the dose of valacyclovir was not adjusted for his renal impairment. At that time, an MRI of the brain was ordered and was found to be normal.

At the same time, CSF was sent for various tests to rule out central nervous system (CNS) infection. The rapid bacterial antigen screen that tests for the common bacterial causes of CNS infection was negative. A viral meningoencephalitis panel that involves antibody testing of all common viral causes of CNS infection was sent. This panel tests for antibodies against several viruses including West Nile virus, western equine encephalitis virus, eastern equine encephalitis virus, Saint Louis encephalitis

CrossMark

To cite: Thind GS, Roach R. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220372

virus, California encephalitis virus, adenovirus, mumps virus, measles virus, cytomegalovirus, influenza viruses, echoviruses and coxsackie viruses. Herpes simplex virus (HSV) and varicella zoster virus (VZV) PCR tests were also ordered. However, these tests had to be sent out for testing and were not expected to result until the next 3–4 days. CSF was also sent for bacterial and fungal cultures as well as acid-fast staining and culture.

DIFFERENTIAL DIAGNOSIS

Acyclovir-induced encephalopathy was high on the differential. However, patient's CSF findings were concerning for viral encephalitis. HSV and VZV were considered as potential aetiologies. HSV is the most common cause of viral encephalitis, whereas VZV encephalitis is a rare complication of herpes zoster infection. This was a particularly difficult situation as the patient was on acyclovir for the treatment of potential viral encephalitis, whereas the same drug was potentially responsible for patient's symptoms.

Other infectious aetiologies were also on the initial differential. Due to the patient's old age, he was at risk for listeria meningoencephalitis. CSF analysis in listeria meningoencephalitis can show lymphocytic predominance.² Tuberculous meningitis can also have a similar CSF analysis; however, the cell count is typically much higher and CSF glucose is usually low.³ Lyme disease was highly unlikely due to absence of history of tick bites or travel to endemic areas. Finally, patient's mentation continued to deteriorate even though he was having regular outpatient dialysis sessions; hence, uraemic encephalopathy was also unlikely. Nonetheless, the overall picture was more consistent with acyclovir-induced encephalopathy. The patient had been receiving six times the recommended dose of valacyclovir, and there was a temporal relationship between the intake of medication and the onset of symptoms.

TREATMENT

All antimicrobials, including acyclovir, were discontinued, and the patient was scheduled for an extended 5-hour dialysis session in an attempt to clear the drug.

OUTCOME AND FOLLOW-UP

The very next day, the patient showed immense improvement in his mental status and was much more wakeful. Thereafter, CSF PCR tests for both HSV and VZV came back negative. The patient had complete recovery and was discharged from the hospital on day 7. In the next few days, all other CSF tests including the viral meningoencephalitis panel, bacterial culture, fungal culture, and acid-fast stain and culture came back negative. This, along with the fact that the patient had rapid improvement in mentation after stopping acyclovir, ruled out CNS infection as the cause of patient's initial presentation. The brisk return of the patient's mentation to baseline also ruled out other non-infectious causes such as primary CNS vasculitis.

DISCUSSION

Valacyclovir is the valyl ester of acyclovir.⁴ It is the oral prodrug of acyclovir with higher bioavailability. Renal elimination accounts for up to 90% of acyclovir clearance. Hence, it is critical that the dosage of these drugs be adjusted in patients with renal impairment, as depicted in [table 1](#). Toxic doses of acyclovir can lead to dose-dependent neurotoxicity. Patients with renal impairment are especially predisposed to acyclovir neurotoxicity. There is some speculation surrounding the precise mechanism of neurotoxicity, but accumulation of the metabolite

Table 1 Recommended valacyclovir dosage based on renal function

Renal function	Recommended valacyclovir dosage
Normal renal function	1 g every 8 hours
CrCl 30–49 mL/min	1 g every 12 hours
CrCl 10–29 mL/min	1 g every 24 hours
CrCl <10 mL/min	500 mg every 24 hours

CrCl, creatinine clearance.

9-carboxymethoxymethylguanine (CMMG) has been implicated. It has been shown that a higher proportion of acyclovir is metabolised to CMMG in patients with renal failure.⁵

Due to paucity of data, the symptom complex of acyclovir neurotoxicity is poorly defined. Confusion and reduced level of consciousness are the most common manifestations. Other symptoms include tremor, dysarthria, agitation and seizures. Symptoms typically start within 24 to 48 hours of taking the first dose. In a case series of 48 patients with acyclovir neurotoxicity, herpes zoster infection was the most common indication for acyclovir therapy, followed by herpes simplex infection.⁶ Of the 44 patients for which age was reported, 30 were more than 50 years old. Twenty four patients had some degree of renal dysfunction: 13 patients were undergoing haemodialysis, 9 were undergoing continuous ambulatory peritoneal dialysis and 2 had mild renal dysfunction not needing dialysis.

Diagnosis of acyclovir neurotoxicity can be difficult. Careful history to establish a temporal relationship between drug intake and onset of symptoms is important. The biggest challenge is distinguishing acyclovir toxicity from viral encephalitis as both of these have overlapping clinical presentations. This is especially relevant when patients are using acyclovir for the treatment of herpes zoster infection, as VZV encephalitis is a potential complication of zoster. Signs of meningismus are indicative of viral encephalitis but are not always present. CSF pleocytosis with mononuclear predominance and high CSF protein are classic findings in viral encephalitis. Acyclovir encephalitis is not typically associated with these abnormalities, and a normal CSF analysis can be an important clue to rule out viral encephalitis. However, it is important to note that CSF lymphocytic pleocytosis and high CSF protein are also non-specific markers of neurovascular inflammation and have been reported in sporadic case reports of acyclovir neurotoxicity as well.⁷

Testing of acyclovir level is not available in most clinical settings and has not been standardised yet. MRI of brain can be normal in early stages of viral encephalitis, and a normal result does not rule it out. PCR testing for HSV and VZV in the CSF offers rapid results with high sensitivity and specificity. However, these tests may not be readily available in all clinical centres. Interestingly, cases of acyclovir neurotoxicity with positive VZV PCR in the CSF have been reported.^{8,9} In a case report by Sacchetti *et al*,⁸ patient's encephalopathy was thought to be due to acyclovir neurotoxicity and the mentation improved on withholding acyclovir. However, PCR for VZV came back positive in the CSF. Nonetheless, acyclovir was continued to be withheld and the patient's neurological status returned to baseline. Hence, sound clinical judgement is required in these scenarios. Apart from the history of renal dysfunction and high dosage of the drug, improvement in neurological status on withholding acyclovir is an important clue in support of acyclovir neurotoxicity.

If acyclovir neurotoxicity is suspected, further administration of the drug should be avoided. Acyclovir is a dialysable molecule, and a 6-hour dialysis session has been shown to remove 60% of

the drug from the circulation.¹⁰ Hence, an extended-session of dialysis and/or more frequent sessions can be considered to facilitate drug removal. Complete recovery can be expected within 5 days of diagnosis. In a clinical review, recovery time from acyclovir neurotoxicity was analysed in patients on haemodialysis and compared with that in patients not on haemodialysis. The duration of acyclovir neurotoxicity was found to be significantly less for patients receiving haemodialysis ($p=0.006$).¹¹

Learning points

- ▶ Acyclovir is renally excreted. The dose of acyclovir and valacyclovir should be adjusted in renal impairment.
- ▶ Supratherapeutic doses of acyclovir or valacyclovir can cause dose-dependent neurotoxicity.
- ▶ Patients with acyclovir neurotoxicity typically have a normal CSF analysis. However, these patients may rarely have CSF lymphocytic pleocytosis and elevated CSF protein, thus closely mimicking viral encephalitis. Careful history taking is of paramount importance.
- ▶ Acyclovir is a dialysable molecule. An extended-session dialysis and/or more frequent sessions can be performed to facilitate drug removal.

Contributors Both authors contributed to the manuscript as follows. RR was part of the primary team who admitted the patient and GST was on the Infectious Disease team, which was consulted for the patient at that time. Hence, both authors were directly involved with patient care. GST did the literature review and manuscript write-up. RR supervised and revised critically for important intellectual content. Both authors gave their final approval of the version to be published.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Perazella MA. Crystal-induced acute renal failure. *Am J Med* 1999;106:459–65.
- 2 Peeters A, Waer M, Michielsens P, *et al*. Listeria monocytogenes meningitis. *Clin Neurol Neurosurg* 1989;91:29–36.
- 3 Chaidir L, Ganiem AR, Vander Zanden A, *et al*. Comparison of real time IS6110-PCR, microscopy, and culture for diagnosis of tuberculous meningitis in a cohort of adult patients in Indonesia. *PLoS One* 2012;7:e52001.
- 4 Jacobson MA. Valaciclovir (BW256U87): the L-valyl ester of acyclovir. *J Med Virol* 1993;(Suppl 1):150–3.
- 5 Helldén A, Lycke J, Vander T, *et al*. The aciclovir metabolite CMMG is detectable in the CSF of subjects with neuropsychiatric symptoms during aciclovir and valaciclovir treatment. *J Antimicrob Chemother* 2006;57:945–9.
- 6 Bates D. Valacyclovir neurotoxicity: two case reports and a review of the literature. *Can J Hosp Pharm* 2002;55:123–7.
- 7 Wade JC, Meyers JD. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann Intern Med* 1983;98:921–5.
- 8 Sacchetti D, Alawadhi A, Albakour M, *et al*. Herpes zoster encephalopathy or acyclovir neurotoxicity: a management dilemma. *BMJ Case Rep* 2014;2014:bcr2013201941.
- 9 De Cauwer H, Maes J, Viaene M, *et al*. Neurological deterioration in the treatment of Herpes zoster: encephalitis or neurotoxic effect of acyclovir? *Acta Neurol Belg* 2017;117:395–7.
- 10 Chowdhury MA, Derar N, Hasan S, *et al*. Acyclovir-induced neurotoxicity: a case report and review of literature. *Am J Ther* 2016;23:e941–3.
- 11 Adair JC, Gold M, Bond RE. Acyclovir neurotoxicity: clinical experience and review of the literature. *South Med J* 1994;87:1227–31.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow