CASE REPORT

Valacyclovir-associated neurotoxicity treated with intensification of peritoneal dialysis

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Accepted 7 July 2017

SUMMARY

We report a 57-year-old woman with end-stage renal disease (ESRD) on maintenance peritoneal dialysis (PD), who presented to the emergency room (ER) by ambulance with complaints of confusion and altered sensorium for 48 hours. She had been reviewed in a walk-in clinic 72 hours earlier and had been prescribed the standard 1000 mg three times per day of valacyclovir for an acute attack of shingles instead of 500 mg once a day on ESRD. In the ER, she received further 500 mg of intravenous acyclovir as herpes encephalitis was clinically suspected. CT of the brain and lumbar puncture were non-contributory to the diagnosis. Valacyclovir and acyclovir were discontinued when the diagnosis of valacyclovir-associated neurotoxicity became clinically evident. As the patient's Glasgow Coma Scale declined, we intensified her PD regimen from one to six exchanges per day and 24 hours later there was a significant neurological improvement.

BACKGROUND

This case is important, as the dose of valacyclovir needs to be adjusted in patients with chronic kidney disease (CKD) and especially in patients with end-stage renal disease (ESRD).

CASE PRESENTATION, TREATMENT, OUTCOME AND FOLLOW-UP

A 57-year-old woman, on peritoneal dialysis (PD) as a consequence of type 2 diabetes, presented with progressive confusion to the emergency room (ER). Her medical history was significant for peripheral arterial disease with a chronic non-infected foot ulcer, hypertension, dyslipidaemia, hypothyroidism and peripheral neuropathy. She was on gabapentin and clonazepam for peripheral neuropathy and restless legs.

A year prior to her presentation, she had been initiated on PD. She was doing extremely well on a single nocturnal exchange of 7.5%, 1.5 L Dianeal fluid. Seventy-two hours prior to her arrival to the ER, she was seen in a walk-in clinic for vesicular, dermatomal, painful rash consistent with shingles and was initiated on valacyclovir therapy at a standard dose of 1000 mg three times per day. Twenty-four hours later, she became confused, refused to mobilise, became irritable and complained of headaches. A day later, she started to have fine tremors and myoclonic jerks which led the family to seek medical attention. On arrival to the ER, vital signs were within normal limits and the Glasgow Coma

Scale (GCS) was documented as 14/15. Clinical examination of the left inner thigh was consistent with a diagnosis of shingles.

In ER, herpes encephalitis was clinically suspected and she received further 500 mg of intravenous acyclovir. A CT scan of the brain showed mild to moderate chronic small vessel ischaemic disease and no obvious intracranial process. She underwent a LP which failed to identify any evidence of encephalitis (colourless, red cell count 1, white cell count <1, glucose 5.6 and protein 0.26). Gabapentin and clonazepam were held but unfortunately, the patient's neurological status continued to deteriorate over the following 24 hours. She became progressively confused, irritable, agitated, ataxic and lethargic and her GCS transiently dropped to 8/15 and was briefly assessed for the safety of her airways by the intensive care team.

Valacyclovir neurotoxicity was suspected when encephalitis was excluded, as the patient had received standard dosing of 1000 mg three times per day, instead of an adjusted dose of 500 mg daily for ESRD. Random acyclovir levels came back as 24 mcg/mL (therapeutic range for oral divided doses of 1200–2400 mg/day of acyclovir; peak level 0.4–2.0 mcg/mL and trough levels 0.14–1.2 mcg/mL). Valacyclovir was held and she was continued on PD (single exchange of 7.5%, 1.5 L) for 48 hours and there was no obvious improvement in her status. Haemodialysis was discussed but it was later jointly decided to intensify the PD regime from one exchange to six exchanges. Twenty-four hours later there was a remarkable improvement in her neurological status and 5 days later she was discharged in a stable state.

INVESTIGATIONS

Complete blood count, electrolytes and renal panel are documented in [tables 1 and 2](#). ECG was unremarkable with normal sinus rhythm with creatine kinase 82 (U/L) and troponin 29 (ng/L). Chest X-ray was grossly normal aside from mild cardiomegaly with minimal interstitial oedema.

A non-contrast CT head revealed chronic small vessel ischaemic disease but no acute intracranial pathology. Blood cultures and urinalysis were eventually non-revealing of infection. Cerebrospinal fluid (CSF) findings were not reflective of encephalitis as shown in [table 2](#) and the analysis of the PD effluent did not show evidence of PD peritonitis.

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To cite: Prasad B, McIsaac M, Toppings J. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220678

Table 1

General Haematology	Level	Reference range
WBC	15.1	4.0–10.0×10 ⁹ /L
Haemoglobin	86	120–160 g/L
Platelets	124	150–400×10 ⁹ /L
Neutrophils	12.3	1.5–6.5×10 ⁹ /L
General chemistry		
Glucose (mmol/L)	7.7	3.6–11.0
Sodium (mmol/L)	129	135–145
Potassium (mmol/L)	3.4	3.5–5.0
Chloride (mmol/L)	93	98–110
CO ₂ (mmol/L)	17	21–30
Anion gap (mmol/L)	23	10–20
Urea (mmol/L)	29.3	3.0–7.1
Creatinine (μmol/L)	746	60–130

CO₂, carbon dioxide; WBC, white blood cell.

DIFFERENTIAL DIAGNOSIS

There were no focal neurological deficits, the differential diagnosis was between herpes encephalitis versus VAN.

DISCUSSION

It is often difficult to distinguish between herpes zoster encephalitis and acyclovir/ valacyclovir neurotoxicity on the basis of clinical findings. However, the sudden onset of neurological or psychiatric symptoms in the absence of headache, fever and focal neurological findings and the presence of normal CSF parameters favour the diagnosis of acyclovir neurotoxicity.

The recommended dosing of valacyclovir for shingles based on the renal function is documented in table 3.

Table 3 Valacyclovir is an oral prodrug of acyclovir, most commonly used to treat herpes simplex virus and varicella zoster virus.^{1,2} Valacyclovir is rapidly converted to acyclovir and amino acid valine through first-pass intestinal and hepatic metabolism, while maintaining a similar efficacy and safety profile. Valacyclovir is typically more pharmacologically favourable on the account of its increased bioavailability compared with acyclovir (55% vs. 15%).³ Therapeutic drug concentrations of acyclovir are more rapidly achieved using valacyclovir compared with acyclovir; while patient satisfaction and compliance are increased using a reduced dosing interval at three versus five times daily.^{3,4}

Valacyclovir is >90% renally excreted after its conversion to acyclovir.^{3,4} As previously stated by Huguenel *et al*, valacyclovir is fecally excreted, whereas acyclovir is renally excreted after first-pass metabolism, which makes individuals with altered renal function particularly susceptible to toxic adverse effects.³ Studies have demonstrated that the half-life of acyclovir, in healthy volunteers with normal renal function, is 2.5–3.3 hours, whereas in patients with ESRD, it can be up to 14 hours which only compounds the toxicity.³

Table 2

CSF	Results	Reference range
Colour	Colourless	
Appearance	Clear	
RBC count	1	0–1×10 ⁶ /L
WBC count	<1	0–5×10 ⁶ /L
CSF differential	Not done	

CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell.

Table 3

CrCl (mL/minute)	Dosage	Duration (days)
>50 mL/minute	1 g three times daily	7
30–49 mL/minute	1 g two times daily	7
10–29 mL/minute	1 g q24h	7
<10 mL/minute	500 mg q24h	7
CAPD	500 mg q24h	7
Haemodialysis	1000 mg q12–24h (after dialysis)	7

CAPD, ; q24h, every 24 hours.

Patients that develop valacyclovir-associated neurotoxicity (VAN) typically present with a constellation of neurological features including, but not limited to, confusion, dysarthria, hallucinations, lethargy, altered level of consciousness, ataxia and death.^{2–5} VAN is typically seen as a result of omission to renally adjusted dosing in those both with ESRD or CKD.^{1,2,5} Neurotoxicity is generally seen with serum acyclovir >3.38 mcg/mL although certain individuals may indeed be susceptible at lower levels.⁴ As previously stated, we empirically treated for suspected VAN and the patient's acyclovir level was ultimately reported at 24 mcg/mL, well above the target trough level of 0.14–1.2 mcg/mL.

If a lumbar puncture (LP) is performed as part of investigations, CSF 9-carboxymethoxymethylguanine (CMMG), an acyclovir metabolite, may also be elevated confirming the diagnosis.^{2,3,6} Although the mechanism of neurotoxicity is poorly understood, one hypothesis is that acyclovir may inhibit mitochondrial DNA polymerase, thereby altering mitochondrial function.³ Interestingly, previous studies have demonstrated that undetectable levels of CMMG in CSF are found in asymptomatic individuals suggesting that CMMG may contribute to neurotoxicity.³ A CMMG level was unfortunately not measured in our patient.

In a patient with non-chronic kidney disease, treatment of VAN includes discontinuation of valacyclovir, with more severe toxicity requiring aggressive intravenous fluid hydration and dialysis in addition to supportive care.^{2,3} In individuals with ESRD, it is imperative to intensify the existing regime. Standard of care should be initiated as per other toxidromes with therapy aimed at supportive care via airway management if indicated.

The current literature states that VAN is best managed with haemodialysis.^{1–5} In our patient, we managed the patient with supportive therapy in addition to intensification of PD. Although, previous studies have demonstrated that haemodialysis is 20 times more efficient than continuous ambulatory PD at removing acyclovir, it was jointly decided to manage with PD alone.^{2,4}

We retrospectively used the Naranjo algorithm, a tool used to discern an adverse drug reaction, to analyse our case presentation. According to this algorithm, our case scored 7 which coincides with 'probable' diagnosis of adverse drug reaction.⁷ We believe that this is supported by clinical improvement and resolution of symptoms with discontinuation of both valacyclovir and acyclovir, in the absence of any alternative diagnosis. Our case shared similarities with Hoskote *et al*, whereby the patient presented with VAN and suffered an acute decline after receiving acyclovir empirically for possible herpes/varicella encephalitis.¹ As previously stated by Hoskote *et al*, it is crucial to differentiate between valacyclovir

neurotoxicity and underlying encephalitis, as empiric treatment for either without confirmation may mitigate a clinical decline.¹

Learning points

- ▶ It is vital that patients with chronic kidney disease or end-stage renal disease are dosed according to the recommended guidelines.
- ▶ Valacyclovir-associated neurotoxicity (VAN) presents with a constellation of neurological features including, but not limited to, confusion, dysarthria, hallucinations, lethargy, altered level of consciousness, ataxia and death delusions.
- ▶ Valacyclovir levels are unlikely to be available in time to assist in clinical decision making and the diagnosis should be on clinical suspicion.
- ▶ Despite being inferior to haemodialysis at removing acyclovir, intensification of the peritoneal dialysis therapy plays a role in treating VAN.

Contributors MI, JT, BP: wrote the draft. BP: revised and edited the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Hoskote SS, Annapureddy N, Ramesh AK, *et al.* Valacyclovir and Acyclovir Neurotoxicity With Status Epilepticus. *Am J Ther* 2016;23:e304–e306.
- 2 Asahi T, Tsutsui M, Wakasugi M, *et al.* Valacyclovir neurotoxicity: clinical experience and review of the literature. *Eur J Neurol* 2009;16:457–60.
- 3 Huguenel C, Felton D, Brucoleri R, *et al.* Case files of the Harvard medical toxicology fellowship: valacyclovir neurotoxicity and unintentional overdose. *J Med Toxicol* 2015;11:132–6.
- 4 Pipili C, Pantelias K, Deda E, *et al.* Intensification of peritoneal dialysis improves valacyclovir neurotoxicity. *Ren Fail* 2013;35:289–90.
- 5 Chaudhari D, Ginn D. Valacyclovir-associated neurotoxicity in peritoneal dialysis patients. *Am J Ther* 2014;21:e215–e217.
- 6 Lee RM, Llewellyn M, Houston A, *et al.* Reversible mental status change and renal dysfunction associated with the use of high-dose oral valacyclovir therapy for acute retinal necrosis. *Retin Cases Brief Rep* 2012;6:266–8.
- 7 Naranjo CA, Busto U, Sellers EM, *et al.* A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239–45.

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