

Received: 2018.06.04
Accepted: 2018.09.07
Published: 2018.12.09

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 1459-1462
DOI: 10.12659/AJCR.911520

Acyclovir Neurotoxicity in a Peritoneal Dialysis Patient: Report of a Case and Review of the Pharmacokinetics of Acyclovir

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEG 1 **Seyed-Ali Sadjadi**
BG 1 **Surakshya Regmi**
EF 2 **Tony Chau**

1 Nephrology Section, Jerry L Pettis Veterans Memorial Medical Center, Loma Linda, CA, U.S.A.
2 Pharmacy Section, Jerry L Pettis Veterans Memorial Medical Center, Loma Linda, CA, U.S.A.

Corresponding Author: Seyed-Ali Sadjadi, e-mail: sadjadia@yahoo.com
Conflict of interest: None declared

Patient: **Male, 80**
Final Diagnosis: **Neurotoxicity due acyclovir**
Symptoms: **Confusion • hallucination**
Medication: **Acyclovir**
Clinical Procedure: —
Specialty: **Nephrology**

Objective: **Unusual clinical course**

Background: The elderly population in the United States and the world is rapidly increasing. With aging, immunity and kidney function decrease, thus predisposing people to viral illnesses for which there is no effective prophylaxis. Herpes zoster afflicts the elderly and other immunocompromised patients, like those with end-stage renal disease, transplant recipients, and cancer patients, causing significant morbidity and sometimes mortality. Treating herpes zoster becomes problematic when the regular pharmacokinetics of the antiviral drugs are disturbed.

Case Report: An 83-year-old African American man with end-stage kidney disease (ESRD) and on chronic peritoneal dialysis (PD) developed herpes zoster, for which he received the manufacturer-recommended intravenous dose of acyclovir. Shortly after taking the medication, he developed confusion, disorientation, and visual hallucinations. He was switched from PD to hemodialysis (HD), with successful recovery. Examination of the cerebrospinal fluid for meningitis and imaging studies of the head were negative. Serum levels of acyclovir were elevated.

Conclusions: Even when the acyclovir dose is properly adjusted for kidney function based on the current manufacturer's recommendations, it can cause neurotoxicity. Here, we discuss the pharmacokinetics of acyclovir and make some recommendations with regard to dose adjustment in patients with ESRD.

MeSH Keywords: **Acyclovir • Dialysis • Neurotoxicity Syndromes**

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/911520>



1703



2



—



9



Background

Acyclovir, an acyclic guanosine nucleoside analogue is an anti-viral agent that is active against herpes virus infections. When prescribed orally, its absorption is poor and only 15 to 30% of the drug is absorbed. However, when given intravenously the total dose enters the circulation, it is picked up by herpes infected cells, converted to an active form, acyclovir triphosphate, incorporated into cell nuclei where it inhibits DNA polymerases. It is widely distributed in body fluids and it is excreted through glomerular filtration and tubular secretion [1]. Use of acyclovir and its congeners, like, valacyclovir and ganciclovir, especially in patients with end stage renal disease can be problematic due to their reduced ability to excrete the drug. These patients are prone to drug toxicity that can cause alteration of mental status and encephalopathy. This can happen in patients with acute or chronic kidney disease not on dialysis [2,3], those on hemodialysis [4,5], peritoneal dialysis [6,7] or patients with a kidney transplant [8]. Although recommendations exist with regard to dose modification with kidney failure, neurotoxicity still happens, when acyclovir dose is not modified for kidney function [9] and even when the dose is appropriately modified, following drug manufacturer and published recommendations [10,11]. Herein we report such a case and review the literature on acyclovir pharmacology and neuro and nephrotoxicity.

Case Report

An 80-year-old African American man with history of arterial hypertension, congestive heart failure and end stage renal disease, on cyclic peritoneal dialysis since 2012, developed pain, and swelling of the left side of his face, involving his left cheek and eye. The pain was radiating down to his jaw, feeling weak and febrile at times. He was seen in the emergency department where he was diagnosed to have impetigo and he was prescribed oral clindamycin and mupirocin cream for local application to the skin lesions. Since there was no improvement in his facial lesions, he was seen in the peritoneal dialysis clinic where he was noted to be alert, awake, afebrile, but he had swelling of the left side of his face including the left periorbital area with no obvious skin vesicles. He said he was very weak and he had no appetite. Due to ambiguity of the clinical picture, he was referred to the infectious disease and dermatology departments. Infectious disease consultant (ID) suspected herpes zoster infection and this impression was confirmed by a dermatologist. He was admitted to the hospital and per ID recommendations, and because of suspicion of encephalitis and possible eye involvement, he was isolated and started on acyclovir at a dose of 5 mg per kg per day intravenously (IV), following drug manufacturer's guidelines and continued on peritoneal dialysis per his usual prescription [12]. Two days later, he was discharged home from the hospital on a renally adjusted

Table 1. Results of CSF fluid examination.

	Patient	Reference
White blood cell count	18	0
Lymphocyte %	87	0
Monocyte %	9	0
Neutrophils %	4	0
Glucose mg/dL	50	40–70
Protein mg/dL	37	15–45
Culture	Negative	Negative

dose of oral acyclovir 200 mg bid, but he came back the next day, with confusion, delusion, disorientation, restlessness and visual hallucinations. Suspecting, acyclovir neurotoxicity vs. herpes encephalopathy, he had a spinal tap that showed clear cerebrospinal fluid (CSF) with elevated white blood cell count, primarily lymphocytes, glucose level of 50 and protein level of 37 mg/dL. He was also switched from peritoneal dialysis to hemodialysis for better drug removal and he was dialyzed on 2 consecutive days for 4 h. The blood and dialysate flow rates were 350 and 600 mL/min, respectively, and the dialyzers used were hollow fiber, high flux, with polysulfone membranes. This was accompanied by rapid improvement in his mental status. Further work up including blood cultures, computed tomographic scan of the head, CSF examination for bacteria and viruses came back negative (Table 1). IV acyclovir was resumed and serum levels of acyclovir were checked. They were found to be elevated at 2.1 and 6.3 mcg/mL (Normal peak level 0.4 to 2 mcg/mL) [13]. Unfortunately, later on during his hospital stay, he developed a seizure episode, fell down from his chair and suffered a subdural hematoma, for which, he underwent surgical evacuation. Fortunately, after a relatively short period of hospitalization and physical rehabilitation he recovered and he was able to be discharged home on hemodialysis treatment.

Discussion

Herpes virus infection, caused by members of the herpes viridae family of viruses, is a common infection in human beings, causing a variety of symptoms. One of these is the herpes zoster-varicella virus, first discovered in 1958, and its complete DNA sequence is well known. The primary infection presents as varicella, mainly in children, which is contagious and from which most patients recover without any major sequelae. After primary infection, the infection becomes dormant in the cranial nerves or posterior root ganglia but can express itself years later, either because of old age, hard work, steroid use, malignancy, human immunodeficiency syndromes, or organ transplantation [14]. Contact with an infected person with herpes

zoster does not cause herpes zoster, but in susceptible individuals it can cause varicella [15]. The disease usually manifests with pain or discomfort in the involved dermatomes, without constitutional symptoms. Most commonly, lumbar, thoracic, and sacral posterior roots are involved, and the 7th nerve and trigeminal nerve are less commonly affected. Initial presentation, however, can be nonspecific, including itching, tingling, and pain, followed by formation of a maculopapular rash that becomes vesiculated and pustulated and finally crusts over. Skin manifestations usually last 2 to 4 weeks and most patients have neuralgia for a few weeks.

Beside skin presentation, herpes zoster can present with encephalitis and ophthalmitis. Eye involvement can be in the form of keratitis, iritis, or episcleritis and these lesions can be sight-threatening. Due to possible complications, herpes virus infections require antiviral treatment that usually consists of either acyclovir or its prodrug, valacyclovir or ganciclovir, with or without simultaneous corticosteroid therapy.

Acyclovir, developed in 1974 [16], has a molecular weight of 225 Daltons and is a 9-2 hydroxy-ethoxy-methylguanine, a nucleoside that is distributed widely in body fluids. Only about 10% to 30% of acyclovir is absorbed after oral administration, and 60% to 90% of it is excreted by the kidneys through glomerular filtration and tubular secretion. It has a half-life of 2 to 3 h in individuals with normal kidney function and 20 h in patients with ESRD [1,17]. Its protein binding is in the range of 9% to 33%. It distributes widely in body fluids and is concentrated in the kidney (100%), cerebrospinal fluid (50%), breast milk (324%), and amniotic fluid and placenta (300% to 600%) [18]. Valacyclovir, a prodrug of acyclovir, has also been associated with neurotoxicity and nephrotoxicity. With increasing renal failure, systemic and renal clearance of acyclovir is reduced and a linear relationship between acyclovir and creatinine clearances has been demonstrated, with a predicted intercept value of 28.7 mL/min/1.73 m² BSA [17]. This is the value of acyclovir clearance in people with anuria and is the basis of acyclovir dose calculation for different levels of kidney function. In addition to the decrease in GFR, decreased tubular secretion (with probenecid) can also increase plasma levels. Plasma levels are measured either by high-performance liquid chromatography or radioimmunoassay. High serum or CSF levels of the main acyclovir metabolite, 9-carboxymethoxymethylguanine (CMMG), are highly predictive of acyclovir neurotoxicity [19]. In a study of the serum levels of CMMG, receiver-operating characteristics curve analysis showed a sensitivity of 91% and specificity of 93% for the development of neuropsychiatric symptoms [20]. Due to its low molecular weight, low protein binding, low volume of distribution (0.6 L/kg), and high water solubility, acyclovir is a good candidate for removal by hemodialysis (Table 2) [21].

Table 2. Factors favoring acyclovir removal by hemodialysis.

Molecular weight	225 Daltons
Protein binding	9 to 33%
Volume of distribution	0.6 L/kg
High water solubility	
Extraction ratio by dialysis	0.45±12

In the study of Krasny et al. [22], 6 anuric patients received 2.5 mg/kg of acyclovir. At the end of 1 h of acyclovir infusion, the mean plasma level was 37.5±24.2 micromoles (8.4±5.4 mcg/mL), twice the level found in patients with normal kidney function. The level was elevated for 47 h in hemodialysis patients but decreased to less than 1 micromole by 11 h in those with normal kidney function. After a 6-h hemodialysis session, with a blood flow rate of 200 mL/min and dialysate flow rate of 300 mL/min, using hollow-fiber dialyzers and single-pass dialysate flow, the extraction ratio was 0.44 and the dialyzer clearance was 113 mL/min. These authors recommended a 50% reduction of the usual daily IV dose in dialysis patients and a supplemental dose after each dialysis session. With higher blood and dialysate flow rates and more efficient dialyzers currently in use in the United States, acyclovir removal could be much higher. Leikin et al. reported a 45% whole-body removal rate with a 3-h session of hemodialysis treatment [13].

Peritoneal dialysis has also been used to treat acyclovir toxicity and some authors advocate intensification of this modality for better drug removal [23,24]. Shah et al., in a study of a single patient on continuous ambulatory peritoneal dialysis, found a total body clearance of 48.3 mL/min/1.73 m² BSA) and a CAPD clearance of 4.3 mL/min. Overall, the CAPD was able to remove less than 10% of the administered dose of the drug [25].

Acyclovir has a high potential for nephrotoxicity and neurotoxicity in patients with reduced kidney function; therefore, dose modification based on kidney function is mandatory, particularly in oliguric [26] and dialysis-dependent patients. The current recommended dose of intravenous acyclovir in patients with ESRD, 5 mg/kg/day, should be further reduced to 2.5 mg/kg/day and preferably be based on ideal and not actual body weight. In case of neurotoxicity in dialysis patients, hemodialysis is the preferred mode of treatment. It provides a better removal rate compared to peritoneal dialysis [27], although the latter is also able to remove acyclovir to some extent [28,29]. Our advice about caution in dosing in renal failure patients extends not only to acyclovir, but also to ganciclovir, valacyclovir, and valganciclovir [26].

Conclusions

Acyclovir is a widely prescribed drug for the treatment of herpes virus infections, particularly when there is risk of cerebral or ophthalmic involvement. It is primarily excreted by the kidneys; therefore, ESRD patients are prone to drug complications even

when it is prescribed according to the manufacturer's dosage recommendations. To avoid neurotoxicity, we recommend an intravenous dose of 2.5 mg rather than the currently recommended dose of 5 mg/kg/day in ESRD patients. In case of neurotoxicity, hemodialysis provides much faster removal of the drug than peritoneal dialysis.

References:

1. Rogers HJ, Fowle ASE: The clinical pharmacology of acyclovir. *J Clin Hosp Pharm*, 1983; 8: 89-102
2. Catalano C, Conforto A: Valacyclovir related neuro and nephrotoxicity in two geriatric patients. *G Ital Nephrol*, 2005; 31: S132-34
3. Delluc A, Mocquard Y, Latour P, Goas JY: Encephalopathy and acute renal failure during acyclovir treatment. *Rev Neurol (Paris)*, 2004; 160(6-7): 704-6
4. Gorlitsky BR, Herion JR: A curious case of confusion in an ESRD patient. *Hemodial Int*, 2017; (3): E58-E62
5. Strumia S, De Mitri P, Bionda E: Neurotoxicity of acyclovir and valacyclovir in a hemodialysis patient. *Eur J Neurol*, 2004; 11(1): 68-69
6. Takayanagi A, Maehana T, Kyoda Y, Yanase M: Neurotoxicity of acyclovir in a peritoneal dialysis patient. *Hinokika Kiyu*, 2010; 56(11): 617-19
7. Chaudhuri D, Ginn D: Valacyclovir-associated neurotoxicity in peritoneal dialysis patients. *Am J Ther*, 2014; 21(6): e215-17
8. Hussein MM, Mooii JM, Al Malki N, Ali Idriss DL: Confusion and agitation after a recent kidney transplantation. *Saudi J Kidney Dis Transpl*, 2008; 19(3): 446-49
9. Onuigbo MA, Nye D, Llovanya PC: Drug induced encephalopathy secondary to non-renal dosing of common medications in two dialysis patients. *Adv Perit Dial*, 2009; 25: 89-91
10. Kageyama R, Hashizumi H: Neurotoxicity induced by the recommended acyclovir dosing in a dialysis patient: A case letter. *J Dermatol*, 2016; 43(3): 339-40
11. Davenport A, Goel S, Mackenzie JC: Neurotoxicity of acyclovir in patients with end stage renal failure treated with continuous ambulatory peritoneal dialysis. *Am J Kidney Dis*, 1992; 20(6): 647-49
12. Hayden FG: Antiviral agents. The pharmacological basis of therapeutics. Goodman and Gilman, 9th edition, 1191-223, McGraw-Hill
13. Leikin JB, Shicker L, Orlovski J et al: Hemodialysis removal of acyclovir. *Vet Hum Toxicol*, 1995; 37(3): 233-34
14. Cohen JJ: Herpes Zoster. *N Eng J Med*, 2013; 369(3): 255-63
15. Leppard B, Naburi AE: Herpes zoster: an early manifestation of HIV infection. *Afr Health*, 1998; 21(1): 5-6
16. King DH: History, pharmacokinetics and pharmacology of acyclovir. *J Am Acad Dermatol*, 1988; 18: 176-79
17. Laskin OL: Clinical pharmacokinetics of acyclovir. *Clin Pharmacokinet*, 1983; 8: 187-201
18. Richards DM, Carmine AA, Brogden RN et al: Acyclovir: A review of its pharmacodynamic properties and therapeutic efficacy. *Drug*, 1983; 26(5): 378-438
19. Gentry JL III, Peterson C: Death delusions and myoclonus: Acyclovir toxicity. *Am J Med*, 2015; 128(7): 692-94
20. Hellden A, Oder-Cederlof O, Diener P et al: High serum concentrations of the acyclovir main metabolite 9-carboxymethoxymethylguanine in renal failure patients with acyclovir related neuropsychiatric side effects: An observational study. *Nephro Dial Transplant*, 2003; 18(6): 1135-41
21. Almond MK, Fan S, Dhillon S et al: Avoiding acyclovir neurotoxicity in patients with chronic renal failure undergoing hemodialysis. *Nephron*, 1995; 69: 428-32
22. Krasny HC, Liao SHT, De Miranda PDE et al: Influence of hemodialysis on acyclovir pharmacokinetics in patients with chronic renal failure. *Am J Med*, 1983; 73(1A): 202-4
23. Prasad B, McIssac B, Toppings J: Valacyclovir associated neurotoxicity treated with intensification of peritoneal dialysis. *BMJ Case Rep*, 2017; 2017: pii: bcr-2017-220678
24. Pipili C, Panthelias K, Deda E et al: Intensification of peritoneal dialysis improves valacyclovir neurotoxicity. *Ren Fail*, 2013; 35(2): 289-90
25. Shah GM, Winer RL, Krasny HC: Acyclovir pharmacokinetics in a patient on ambulatory peritoneal dialysis. *Am J Kidney Dis*, 1986; 7(6): 507-10
26. Almond MK: Acyclovir and valacyclovir neurotoxicity in patients with renal failure. *Nephrol Dial Transplant*, 2003; 18(12): 2680; author reply 2680-81
27. Khambampati G, Pakkivenkata U, Kazory A: Valacyclovir neurotoxicity can be effectively managed by hemodialysis. *Eur J Neurol*, 2011; 18(3): e33
28. Okada T, Nakao T, Matsumoto H et al: Valacyclovir neurotoxicity in a patient with end stage renal disease treated with continuous ambulatory peritoneal dialysis. *Clin J Nephrol*, 2002; 58(2): 168-70
29. Izzedine H, Mercadal L, Aymard G et al: Neurotoxicity of acyclovir in peritoneal dialysis: A pharmacokinetic study. *Am J Nephrol*, 2001; 21(2): 162-64