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Resolution of acyclovir-associated neurotoxicity with the aid of improved clearance estimates using a Bayesian approach: a case report and review of the literature

Whitney A. Watson, PharmD, BCPS[1], **Nathaniel J. Rhodes, PharmD, MSc BCPS**[1,2], **Ignacio A. Echenique, MD**[3], **Michael P. Angarone, DO**[4], and **Marc H. Scheetz, PharmD, MSc, BCPS-AQ ID**[1,2,*]

[1]Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA

[2]Department of Pharmacy Practice, Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA

[3]Department of Infectious Disease, Cleveland Clinic Florida, Weston, FL, USA

[4]Division of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Summary

What is known and objective—Neurotoxicity is a side effect of acyclovir. We report the first case, to our knowledge, whereby Bayesian-informed clearance estimates supported a therapeutic intervention for acyclovir-associated neurotoxicity.

Case summary—A 62 year-old male with the diagnosis of disseminated zoster was being treated with intravenous (IV) acyclovir when he developed symptoms of acute neurotoxicity. Acyclovir had been dose-adjusted for renal dysfunction according to traditional creatinine clearance estimates; however, since the patient was also on vancomycin, Bayesian estimates of vancomycin clearances were performed, which revealed a 2-fold lower creatinine clearance. In response to the Bayesian estimates, acyclovir was discontinued, and improvements in mentation were noted within 24 hours.

What is new and conclusion—Alternate approaches to estimate renal function beyond Cockcroft-Gault, such as a Bayesian approach used in our patient, should be considered when population estimates are both likely to be inaccurate and potentially dangerous to the patient.

What is known and objective—Acyclovir is highly efficacious in the treatment and prophylaxis of varicella zoster and herpes simplex viral infections. Accumulation of acyclovir (1) and valacyclovir (2) have been associated with neurotoxocity, manifesting as worsening of mental status, in some cases hallucinations, agitation, or lethargy (1, 3). Most reports that describe acyclovir-associated neurotoxicity coincide with renal dysfunction in the affected patient, as

[*]**Corresponding author and reprint requests:** Marc H. Scheetz, PharmD, MSc; Associate Professor of Pharmacy Practice; Midwestern University Chicago College of Pharmacy; 555 31st St., Downers Grove, IL 60515, Phone: 630-515-6116; Fax: 630-515-6958; mschee@midwestern.edu.

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acyclovir is eliminated primarily through excretion in the urine (4, 5). Renal dysfunction appears to be a strong predictor of acyclovir-associated neurotoxicity as it is thought to potentiate the risk for neurotoxicity. However, the exact exposure-toxicity relationship for acyclovir-associated neurotoxicity has not been well defined (6–8).

Keywords

acyclovir; adverse effects; pharmacodynamics; pharmacokinetics; statistical model

Previous studies have identified a relationship between acyclovir exposure and neurotoxicity. Case reports indicate that acyclovir-induced neurotoxicity can manifest within 1–2 days after patients' experience of supra-normal acyclovir concentrations, and sometimes as early as within a few hours after a single dose. Other cases failed to demonstrate a clear relationship between acyclovir exposure and toxicity (4, 9, 10). Given the timeframe of toxicity from these studies, peak blood concentrations (i.e., Cmax) or average daily drug exposure (as measured by the area under the concentration-time curve; i.e., AUC) may predict the onset of neurotoxicity.

As acyclovir clearance is closely related to creatinine clearance, changes in renal function must be closely monitored during acyclovir therapy in order to avoid potentially neurotoxic accumulation of the parent drug or its metabolites. Several studies have shown that as renal function declines, a larger proportion of the parent drug is converted to the 9-carboxymethoxymethylguanine (CMMG) metabolite. Likewise, increased peripheral plasma acyclovir concentrations have been associated with increased exposure to both CMMG and the parent drug in the CNS (9, 11, 12). Hence, renal impairment can lead to a decrease in the total body clearance of acyclovir: resulting in higher acyclovir and CMMG 24-hour steady state AUC and Cmax in both the plasma and the CSF. The usefulness of these relationships is highlighted by the implementation of therapeutic drug monitoring programs. Clinicians have monitored CMMG concentrations as a surrogate measure of neurotoxicity (11–14). Hellden et al. describe a positive correlation between the incidence of neurotoxicity and detectable concentrations of CMMG in the CSF in patients treated with either acyclovir or valacyclovir (12).

Obtaining unbiased and timely estimates of creatinine clearance in acutely ill patients presents a clinical challenge. Here, we describe a case of an immunocompromised host with presumed disseminated varicella zoster virus (VZV) infection complicated by probable acyclovir-associated neurotoxicity. The patient's clinical course was also complicated by Gram-positive bacteremia necessitating vancomycin therapy. When calculated standard creatinine clearance estimates for our patient were questioned because of the patient's acute on chronic renal dysfunction, we used Bayesian estimates of vancomycin clearance and previously published relationships between renal clearance and vancomycin clearance to modify acyclovir therapy. Dose and schedule adjustment of acyclovir were associated with abatement of neurologic signs of toxicity.

Case Description

Clinical data (e.g. drug administration, microbiology reports, clinical chemistry) were obtained from the electronic medical record. A case report exemption was obtained from the Northwestern University Institutional Review Board.

A 62-year-old Caucasian male presented to an outside facility with complaints of diarrhea, poor oral intake, and weight loss. The patient's past medical history was significant for a history of Goodpasture syndrome complicated by end-stage renal disease requiring a living donor kidney transplant eleven years prior to presentation, chronic allograft glomerulopathy, and a recent diagnosis of collagenous colitis. Prior to admission to the outside facility, the patient had received a fourteen-day course of oral valacyclovir for presumed dermatologic VZV reactivation; however, he was not experiencing neurotoxic symptoms at that time. Physical exam findings at the outside facility were concerning for evolving lesions, and the patient was started on intravenous (IV) acyclovir two days prior to transfer. Mental status changes from baseline and confusion were noted within 48 hours following initiation of IV acyclovir. The patient was subsequently transferred to our facility for further evaluation and management.

Upon transfer to our facility, examination was notable for hypovolemia and altered mental status (e.g., oriented to person and city, but not date, state, or situation). Vesicular skin lesions were identified diffusely throughout the patient's cervical, thoracic, and lumbar back, with active drainage, with additional erythematous, encrusted lesions on his abdomen. Neurologic examination was notable for asterixis and brisk reflexes. Serum creatinine was 2.5 mg/L (baseline of 1.8 mg/dL). Despite recent weight loss, the patient maintained a Body Mass Index (BMI) of 20.1 kg/m^2. A urinalysis was significant for >10 hyaline casts with proteinuria, and a renal ultrasound revealed mild-transplant hydronephrosis with some peri-nephric fluid. The patient was continued on IV acyclovir for presumed disseminated VZV dosed at 12.1 mg/kg every 12 hours (in accordance to our hospital protocol and adjusted for a calculated creatinine clearance of 26 mL/min) (10). Rapid shell viral culture and direct fluorescent antibody testing performed on actively draining lesions, were ultimately negative for herpes simplex virus and VZV. Although lumbar puncture was considered for evaluation of VZV meningoencephalitis, nuchal rigidity was absent, Kernig's and Brudzinski's signs were negative. Further, there were active rash lesions overlaying the lumbar spine. Thus, the procedure was initially deferred.

On hospital day +3, two sets of blood cultures turned positive with Gram-positive cocci. The patient was empirically initiated on vancomycin IV (dosed at 15 mg/kg every 18 hours). That same day, the patient's mental status notably declined. On hospital day +4, the patient was disoriented and had waxing and waning mental status. On hospital day +5, the patient was found to have a flat affect and was minimally responsive except to loud or painful stimuli. On hospital day +6, the patient was non-verbal and somnolent. In response to the patient's declining mental status, a lumbar puncture was performed on day +5. The cerebrospinal fluid (CSF) examination revealed 37 white cells with lymphocytic predominance, and a VZV polymerase chain reaction amplification test on CSF fluid revealed 912 copies/mL of VZV (Table 1).

In light of the clinical and positive virologic findings and progressively worsening mental status, viral encephalitis could not be excluded at the time. However, in the setting of therapeutic doses of acyclovir and Bayesian predictions of poor renal function, we maintained a higher clinical suspicion for acyclovir toxicity over inadequately treated VZV encephalitis. Therefore, on day +6, our team recommended temporary discontinuation of the IV acyclovir, and further doses were held.

On day +7, the patient was observed to have marked improvement in mental status including increased responsiveness, improved dysarthria, and appropriate behavior. After the patient's mentation improved, he recalled visual hallucinations in the previous days, specifically red coloration of room and walls. By hospital day +11, mental status returned to baseline. Valacylovir was ultimately resumed to complete a 21-day course of valacyclovir (dose adjusted to 1000mg twice daily) for possible meningoencephalitis and dermatomal VZV, during which mentation remained stable. Over this period, the previous gram-positive cocci was ultimately identified to be *Staphylococcus aureus*. Echocardiography was consistent with mitral valve endocarditis, prompting a six-week course of vancomycin therapy.

Traditional and Bayesian estimates of renal clearance and resolution of altered mental status

Our recommendation to cease acyclovir dosing was based on our suspicion that the serum creatinine and Cockcroft-Gault (10) calculated creatinine clearance (Table 1) were not representative of the patient's glomerular filtration rate. While real-time assessment of acyclovir pharmacokinetics may have most accurately classified our patient's acyclovir exposure, access to an acyclovir assay was not available at our institution. Additionally, acyclovir levels have been shown to not always correlate with neurotoxicity (4, 15). Therefore, vancomycin trough concentrations were assessed as a surrogate estimate of glomerular filtration vis-à-vis acyclovir clearance in this patient.

Using a 2-compartment vancomycin population pharmacokinetic model available within the MM-USC*PACK software BestDose® (Laboratory of Applied Pharmacokinetics, University of Southern California) Version 1.110 as the Bayesian prior, we fitted the patient's observed vancomycin concentrations, clinical covariates (e.g., serum creatinine and weight), and vancomycin doses to obtain posterior parameter estimates (i.e., volume of distribution, intercompartmental transfer rates, and the elimination rate). Vancomycin elimination was proportionalized to creatinine clearance using the equation: $K_{vanc} = K_{int} + (CrCL\ [mL/min/1.73m^2] \times K_{slope})$ where K_{int} was fixed at 0.002043 hr^{-1}. Distribution volume was scaled to total body weight. Of the 18 sets of pharmacokinetic parameters in the final model joint-probability distribution, the Bayesian software identified the set of parameters that minimized the average weighted-squared error between the observed data and the fitted data.

The patient had received three doses of vancomycin at the time of the assessment. Three sequential vancomycin serum concentrations were obtained after the third dose. The vancomycin elimination rate constant (K_{el}) was calculated from the 3 sequential concentrations using traditional pharmacokinetic formulae (Table 2) (16). Traditional vancomycin elimination rate constant estimates ranged from 0.0131 to 0.0117 h^{-1}, with total

clearance rates ranging from 7.2 to 8.1 mL/min and Bayesian estimated creatinine clearances of 5.1 to 6.4 mL/min using previously published regressions of vancomycin clearance on estimated creatinine clearance across varying degrees of renal dysfunction [i.e., $(CL_{vanc} - 3.66)/0.689 = CrCL$] (17). In contrast, the patient's Cockcroft-Gault estimated creatinine clearance was 27.3 mL/min. The Bayesian-informed model of vancomycin consisted of a weighted average of the most-likely set of pharmacokinetic parameters from the joint-probability distribution. The mean (SD) model-predicted vancomycin volume of distribution was 0.58 (9.4×10^{-5}) L/kg, and the mean (SD) model-predicted elimination rate constant was 8.4×10^{-4} (2×10^{-10}) h^{-1}. The Bayesian-informed estimates of total vancomycin clearance ranged from an average of 15.0–19.1 mL/min during vancomycin therapy, or about two-fold higher than estimates obtained from traditional equations (Table 2). Thus, while the clearance estimates were different, both traditional and Bayesian-informed approaches to estimating renal clearance from vancomycin clearance supported the supposition that our patient's renal clearance was significantly impaired. Using the traditional PK estimates to solve for CrCL using established regressions, the patient's creatinine clearance approximately 5-fold lower than that predicted by the Cockcroft-Gault method (i.e., 5.1 mL/min [traditional PK estimate] vs. 27.3 mL/min [Cockcroft-Gault estimate]). Though less dramatically different, the Bayesian PK estimates corresponded to a solved creatinine clearance in our patient approximately 0.6-fold lower compared to that determined using the Cockcroft-Gault calculation (i.e., 16.5 mL/min [Bayesian estimate] vs. 27.3 mL/min [Cockcroft-Gault estimate]). Cockcroft-Gault estimates of renal clearance appeared to exhibit low precision in our patient since it relies on population values for serum creatinine production and is not individually specific for estimates of renal function, especially among patients with rapidly changing renal function.

What is new and conclusion

To our knowledge, this is the first case of acyclovir-associated neurotoxicity wherein a Bayesian-informed estimate of renal clearance was utilized to support a therapeutic intervention, in this case: discontinuation of IV acyclovir therapy. Bayesian estimates of creatinine clearance suggested that our dosing intensity was much higher than recommended for our patient's level of renal dysfunction. It should be noted that while acyclovir undergoes clearance by both glomerular filtration and tubular secretion (17, 18), dosing recommendations are based on creatinine clearance: a clinical tool used to estimate glomerular filtration. At present, there is no simple method by which to measure the extent of tubular secretion in the clinical setting, but when patient glomerular filtration is lower than standard glomerular filtration, it is assumed that tubular secretion may also be adversely affected (19). The discordance that we observed between standard creatinine clearance calculations and Bayesian estimations of vancomycin clearance vis-à-vis glomerular filtration supported our clinical suspicion that our patient's overall renal capacity was below that predicted by standard population-based equations. Bayesian estimates of vancomycin clearance are more precise at the patient-level, whereas Cockcroft-Gault calculations rely on population estimates and values. We encourage the use of patient-level estimates when population-based estimates are in doubt.

The adverse neurologic effects of high-dose acyclovir and valacyclovir have been well-described (2, 4). The literature describes highly varied manifestations of acyclovir-associated neurotoxicity including: tremor, myoclonus, seizures, dysarthria, ataxia, hallucinations, delirium, or coma. Further, diffuse electroencephalographic abnormalities and increased concentrations of myelin basic protein in the CSF have been observed (20–22). Our patient experienced many of the symptoms temporally-associated with high dose acyclovir. The rapid resolution of our patient's symptoms after acyclovir discontinuation supports a causal effect (Naranjo score = 5, probable association) whereas progressive VZV encephalitis was less likely the cause of his acute episode of neurologic dysfunction (23).

Along with renal dysfunction, drug interactions may have contributed toward the suspected toxicity of acyclovir. The patient's immunosuppressant regimen for their renal transplant included mycophenolate mofetil and tacrolimus. Concomitant use of acyclovir and mycophenolate mofetil can result in competition for tubular secretion, leading to reduced acyclovir clearance and increased Cmax and AUC (24). Tacrolimus and acyclovir have both been associated with nephrotoxicity, and warrant caution when combined with other potentially nephrotoxic agents (5, 25). Thus, our patient may have experienced decreased acyclovir clearance in the setting of renal toxicity due to receipt of multiple concomitant nephrotoxins.

In conclusion, acyclovir-associated neurotoxicity was detected in a patient for whom Cockcroft-Gault estimates of renal function poorly predicted vancomycin clearance. Vancomycin clearance was calculated using traditional and Bayesian approaches as a clinical estimate of acyclovir clearance. Using the Bayesian estimated clearance, a modified drug-dosing regimen was applied after abatement of the patient's neurotoxic symptoms. As true renal function may not correlate renal function estimates, alternate approaches to estimate renal function beyond Cockcroft-Gault, such as the Bayesian approach used in our patient, may be necessary to minimize the likelihood of toxicity.

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Table 1

Clinical course of neurotoxicity and patient covariates at our facility

Date	Mental status	Imaging	Laboratory and microbiology findings	SCr (mg/dL)	CrCl (Cockcroft-Gault) (mL/min)
Hospital day 0	Oriented to person, city, but not oriented to date, state or situation.	CT brain XR chest Renal ultrasonography	-Skin herpes simplex and VZV DFA negative -Rapid shell viral culture negative for herpes simplex and VZV -Urinalysis: Specific gravity 1.017, protein screen positive, glucose screen negative, no ketones, trace blood, 2–5 granular casts, >10 hyaline casts, 0 WBC, 0 RBC -Urine culture: 2,000 cfu/ml Gram Negative Rods	2.54	26.44
Hospital day 1	Fluctuating mental status	CT spine MR brain		2.52	26.65
Hospital day 2	Somnolent, slightly more confused. After a few attempts was able to give his own name. Not oriented to location. Followed some commands but resisted exam.	EEG	Blood cultures: MSSA	2.42	27.75
Hospital day 3	Inappropriate reactions (e.g. hiding under bedsheets)	CT abdomen, chest, pelvis		2.36	28.46
Hospital day 4	Alert and oriented × 0–1 to self. Mental status and ability to follow commands progressively declining		-Skin Herpes simplex and VZV DFA negative -Rapid shell viral culture negative for herpes simplex and VZV	2.35	28.58
Hospital day 5	Disoriented, flat affect, non-verbal, minimally responsive to vocal cues, responsive to painful stimuli and loud voice only.		CSF cell count with differential: 37 WBC (83% lymphocytes, 15% monocytes, 1% macrophages, 1% neutrophils); 4 RBC CSF glucose: 90 CSF gram stain and culture: gram stain negative, culture with no growth at 72 hours CSF protein: 72 CSF VZV PCR: 912 copies/mL Blood glucose: 146	2.36	28.46
Hospital day 6	Non-verbal, somnolent	MRA head MR spine		2.51	26.76
Hospital day 7	Awake and interactive, follows commands and responding to verbal cues, albeit mostly with inappropriate responses. Notes earlier hallucinations and red vision (“only seeing things in red”)			2.41	27.87

Date	Mental status	Imaging	Laboratory and microbiology findings	SCr (mg/dL)	CrCl (Cockcroft-Gault) (mL/min)
Hospital day 8	Fully alert and oriented this morning, more interactive			2.21	30.39
Hospital day 9	Patient is fully oriented, alert and communicative	Transesophageal echocardiography		1.99	33.75
Hospital day 10	Alert and oriented, more confluent speech with less word finding			1.96	34.27

** All CTs and MRs were done without contrast dye. All creatinine clearances calculated using weight of 62kg.

Abbreviations: CSF: cerebral spinal fluid; DFA: direct fluorescent antibody; Echo: Echocardiogram; EEG: Electroencephalography; MR: Magnetic Resonance; MSSA: methicillin-sensitive *Staphylococcus aureus*; PCR: polymerase chain reaction; RBC: red blood cells; VZV: Varicella zoster virus; WBC: White blood cells; XR: X-Ray

Table 2

Comparison of pharmacokinetic parameter estimates from traditional and Bayesian informed pharmacokinetic model.

Estimation scheme	**Hospital Day**	**Weight (kg)**	**CrCl (mL/min/1.73m2)**	**K_{el} (h-1)**		**V_d (L/kg)**	**Cl_{vanc} (mL/min)**	**Cl_{renal} (mL/min)**
Traditional	Day +5	61.5	27.3	0.0131		0.6	8.1	6.4
	Day +6	61.5	27.3	0.0117		0.6	7.2	5.1
Estimation scheme	Hospital Day	Weight (kg)	CrCL (mL/min/1.73m2)	K_i (h-1)	K_s (h-1)	V_d (L/kg)	Cl_{vanc} (mL/min)	Cl_{renal} (mL/min)
Bayesian-informed	Day +3	61.5	27.5	0.002043	0.000843	0.585	15.1	16.6
	Day +4	61.5	27.3	0.002043	0.000843	0.585	15.0	16.5
	Day +5	61.5	27.3	0.002043	0.000843	0.585	15.0	16.5
	Day +10	61.5	35.3	0.002043	0.000843	0.585	19.1	22.3
	Day +11	61.5	34.7	0.002043	0.000843	0.585	18.8	21.9
	Day +13	61.5	34.1	0.002043	0.000843	0.585	18.5	21.5
	Day +14	61.5	34.5	0.002043	0.000843	0.585	18.6	21.7
	Day +16	61.5	34.5	0.002043	0.000843	0.585	18.6	21.7
	Day +18	61.5	34.9	0.002043	0.000843	0.585	18.8	22.0

Abbreviations: Cl_{renal} = renal clearance; Cl_{vanc} = clearance of vancomyin; CrCl = creatine clearance; kg = kilogram; K_i= elimination rate intercept; K_s = elimination rate slope; mL= milliliter; min= minute; V_d = volume of distribution