

Valacyclovir Neurotoxicity: Two Case Reports and a Review of the Literature

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ABSTRACT

Valacyclovir is a prodrug of acyclovir. Headache is the most common central nervous system side effect of acyclovir. Elderly patients and people with chronic renal failure are most susceptible to the neurotoxic effects of acyclovir, which usually manifest as confusion, hallucinations, dizziness, irritability, ataxia, tremor, myoclonus, and seizures. The symptoms usually occur within 3 days of initiation of therapy and resolve within 5 days after discontinuation. The results of lumbar puncture and computed tomography of the head are essentially unremarkable. Levels of acyclovir in the plasma do not correlate with the toxic effects experienced. The most common electroencephalographic abnormality is diffuse generalized slowing of brain wave activity. Two cases of valacyclovir neurotoxicity are presented, along with a review of the literature on acyclovir neurotoxicity.

Key words: valacyclovir, acyclovir, neurotoxicity, confusion, hallucinations, dizziness, irritability, ataxia, tremor, myoclonus, seizures

RÉSUMÉ

Le valacyclovir est un biomédicament de l'acyclovir. Les céphalées représentent l'effet indésirable sur le système nerveux central le plus courant de l'acyclovir. Les patients âgés et les personnes atteintes d'insuffisance rénale chronique sont les plus sensibles aux effets neurotoxiques de cet agent, qui se manifestent sous les formes suivantes : confusion, hallucinations, étourdissements, irritabilité, ataxie, tremblements, myoclonies et convulsions. Les symptômes surviennent habituellement dans les trois jours suivant le début du traitement et se résorbent dans les cinq jours suivant son interruption. Le liquide céphalo-rachidien et les clichés de la tomographie cérébrale ne révèlent essentiellement rien de particulier. Les taux plasmatiques de l'acyclovir ne présentent pas de corrélation avec les effets toxiques éprouvés. L'altération électroencéphalographique la plus courante est une réduction diffuse de l'activité cérébrale. Deux cas de neurotoxicité au valacyclovir sont présentés avec une analyse de la littérature sur ce type de neurotoxicité.

Mots clés : valacyclovir, acyclovir, neurotoxicité, confusion, hallucinations, étourdissements, irritabilité, ataxie, tremblements, myoclonies, convulsions

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INTRODUCTION

Valacyclovir is a prodrug of acyclovir and therefore shares a similar side effect profile. Headache is the most common central nervous system side effect. Elderly patients and those with chronic renal failure are most susceptible to adverse effects of the central nervous system, such as confusion, hallucinations, dizziness, irritability, ataxia, tremor, myoclonus, and seizures.¹⁻⁴ Two suspected cases of neurotoxicity associated with valacyclovir are presented here, along with a review of the literature regarding acyclovir neurotoxicity.

CASE REPORT

Case 1

A 65-year-old man was brought to hospital after his wife found him in a confused state. He thought that strangers were in the house when he and his wife were alone, and he complained that the telephone and television were not working when in fact his wife found that they were in perfect order.

His medical history included type 1 diabetes mellitus, chronic renal failure, heart failure, peptic ulcer disease, hypertension, depression, transient ischemic attacks, dyslipidemia, and a below-the-knee amputation



of the left leg. Three years previously he had been admitted to the intensive care unit with bronchiolitis obliterans organizing pneumonia complicated by confusion. He had been re-admitted 1 month later with confusion, which had resolved within 7 days. The confusion might have been due to the steroids used to treat the pneumonia. Upon discharge the patient experienced difficulties with calculations and learning new information.

Medications at the time of the current admission included simvastatin 10 mg daily, senna 8.6 mg bid, docusate sodium 50 mg bid, nitroglycerin patch 0.4 mg/h for 12 h daily, calcium carbonate 1250 mg tid, docusate calcium 240 mg daily, erythropoietin 4000 units SC on Mondays, Wednesdays, and Fridays, felodipine 10 mg daily, renal multiple-vitamin supplement daily, acetylsalicylic acid 325 mg daily, sertraline 25 mg daily, regular human insulin 30/70 units bid, and lactulose and nitroglycerin spray prn. Valacyclovir 1 g bid had been initiated 36 h before the admission for treatment of herpes zoster.

On examination the patient was alert and oriented to person and place but not time. He had diminished concentration and was incoherent. His result on the Mini-Mental State examination was 13/30. His blood pressure was 153/76 mm Hg, heart rate 95 beats/min, respiratory rate 20 breaths/min, and temperature 37°C. He had small erythematous macules on the right subscapular region.

Serum electrolyte and glucose concentrations were normal, except for serum carbon dioxide 20 mmol/L (normal range 22 to 28 mmol/L), serum phosphate 1.97 mmol/L (normal range 0.8 to 1.5 mmol/L), serum urea 26.8 mmol/L (normal range 3 to 9 mmol/L), and serum creatinine 442 µmol/L (normal range 60 to 120 µmol/L). The corrected serum calcium concentration was in the upper normal range. His serum hemoglobin concentration was slightly below normal, at 116 g/L (normal range 140 to 180 g/L). The remainder of the complete blood cell count was within normal limits. Serum thyroid-stimulating hormone, vitamin B₁₂, and folate concentrations were normal. A lumbar puncture revealed a white blood cell count of 0.6 × 10⁶/L (normal range 0 to 5 × 10⁶/L), protein concentration of 0.81 g/L (normal range 0.15 to 0.45 g/L), and glucose concentration of 4.7 mmol/L (normal range 2.8 to 4.4 mmol/L) (serum glucose concentration was 8 mmol/L [normal range 3.6 to 11.1 mmol/L]). No organisms were observed on gram staining, and no fungal or yeast elements were seen on a direct smear. Screening for bacterial and cryptococcal antigens and the results of viral cultures were all negative. A Venereal Disease Research Laboratory test for syphilis

serology was unreactive. Computed tomography of the head did not reveal any abnormalities. Electroencephalography showed some global swelling consistent with central nervous system toxic effects.

Valacyclovir was discontinued upon admission to hospital. It was suspected that acyclovir neurotoxicity had developed after two 1-g doses of valacyclovir, although the dosage of valacyclovir (1 g bid) was appropriate for the calculated creatinine clearance (approximately 20 mL/min). The patient remained afebrile over the next 48 h and was discharged home with baseline level of functioning.

Case 2

A 44-year-old man presented to the Emergency Department with a 2-day history of disorientation, confusion, ataxia, dysarthria, and photophobia. His medical history included Wegener's granulomatosis with chronic renal failure (serum creatinine concentration stable at approximately 230 µmol/L) and hypertension.

One week before admission the patient had developed a herpes zoster infection. Valacyclovir 1 g tid was prescribed, and his prednisone and cyclophosphamide were discontinued. He completed 5 days of therapy before presenting to the hospital.

On examination he was afebrile and hypertensive (blood pressure 186/124 mm Hg). His heart rate was 92 beats/min and his respiratory rate 18 breaths/min. The results of a physical examination, including evaluation of the cranial nerves, were normal and he scored 5/5 on a strength test of the extremities. Serum electrolyte and glucose concentrations were normal, except for serum creatinine 415 µmol/L and serum urea 16.8 mmol/L. The corrected serum calcium concentration was within the normal range. The complete blood count revealed a normal white blood cell count, serum hemoglobin concentration of 127 g/L, and a platelet count below normal, at 115 × 10⁹/L (normal range 150 to 440 × 10⁹/L). Lumbar puncture revealed a white blood cell count of 51.3 × 10⁶/L, protein concentration of 0.70 g/L, and glucose concentration of 3.2 mmol/L (serum glucose concentration was 5.7 mmol/L). No organisms were seen on gram staining, and no fungal or yeast elements were seen on a direct smear. Cultures of blood and urine were negative. Screening for bacterial and cryptococcal antigens was negative, as were viral cultures and polymerase chain reaction for herpes simplex virus. Computed tomography and magnetic resonance imaging of the head revealed no abnormalities. It was thought that the patient might have been experiencing a neurological exacerbation of Wegener's



granulomatosis, but neutrophil staining was negative, and concentrations of antineutrophilic cytoplasmic antibodies ([p-ANCA] Anti-MPO 2 KEU/L [0–5 KEU/L] and [c-ANCA] Anti-PR3 2 KEU/L [0–5 IKEU/L]) were within the normal range.

After admission, losartan, metoprolol, and clonidine were initiated to control the patient's blood pressure. He received ampicillin 2 g IV q6h and ceftriaxone 2 g IV q12h for 24 h. He also received acyclovir 720 mg IV q12h for 2 doses, followed by 1 dose of 500 mg, after which the topical ointment was administered. The IV acyclovir was discontinued because of suspicion of acyclovir neurotoxicity. The patient's neurological status had not improved since admission, his speech was slurred, and he told the nursing staff he thought he was dead. Over the next 24 h he received 5 doses of haloperidol IM, ranging from 2.5 to 5 mg. Within 24 h after discontinuation of the acyclovir, his neurological status began to improve, with lessening of confusion and resolution of psychosis. Over the next 72 h he became afebrile and returned to his baseline level of functioning.

Table 1. Characteristics of Patients Experiencing Neurotoxic Effects of Acyclovir^{3,4, 8-34} and Valacyclovir^{35,36}

| Patient Characteristic | No. of Patients* |
|--------------------------------|---|
| Sex† | |
| Female | 26 |
| Male | 18 |
| Age (years) | |
| Range | 5–80 |
| Mean | 52 |
| Route of administration | |
| Oral | 20 |
| IV | 25 |
| Dose | |
| Oral | 200 mg daily to 800 mg 5 times daily (mean 1858 mg/day) |
| IV | 4 mg/kg daily to 50.4 mg/kg daily (mean 20.5 mg/kg daily) |
| Symptoms | |
| Renal dysfunction | 24‡ |
| Onset of symptoms | Usually within 72 h§ |
| Resolution of symptoms | Usually within 5 days¶ |

*Except where indicated otherwise

†In one case, the sex and age of the patient were not reported.

‡Thirteen patients were undergoing hemodialysis, 9 were undergoing continuous ambulatory peritoneal dialysis, and 2 had mild renal dysfunction.

§Onset of symptoms rarely occurred after 1 week.

¶Some patients required 6 to 16 days to return to baseline functioning.

LITERATURE REVIEW

Forty-six cases of acyclovir neurotoxicity³⁻³⁴ and 2 cases of valacyclovir neurotoxicity^{35,36} were reviewed (Table 1). Three cases of acyclovir neurotoxicity were not included in the analysis presented here because there were other possible causes of the neurotoxicity: psychiatric illness,⁵ lupus cerebritis,⁶ and normeperidine accumulation.⁷ Herpes zoster infection was the most common indication for acyclovir therapy, followed by herpes simplex infection. Thirty of the 44 patients for whom age was reported were over 50 years of age (Table 1). Twelve of the patients had cancer, and approximately half had received an inappropriate dose of the drug (according to renal function). Concurrent medications were reported in 29 of the 45 cases. Some patients were receiving medication with known central nervous system side effects, including opioids, benzodiazepines, neuroleptics, interferon, and prednisone, but doses and frequencies were not consistently reported. There were various manifestations of the acyclovir neurotoxicity (Table 2).

The analysis of cerebrospinal fluid was reported as normal in most cases. Abnormalities of the cerebrospinal fluid included elevated protein (0.48 to 1.85 g/L, mean 0.79 g/L)^{3,14,15,17,22} and pleocytosis (leukocytes 2 to 32 x 10⁶/L [mean 12.5 x 10⁶/L] with 70% to 95% lymphocytes^{3,4,20,22,30,34}). Cultures of blood and cerebrospinal fluid were negative in all cases.

The findings on cranial computed tomography were essentially unremarkable. In one case this imaging modality showed multiple areas of diminished density in the periventricular white matter 6 days after discontinuation of acyclovir.⁴ Magnetic resonance imaging displayed abnormal signs from multiple areas, including the cerebellum, the pons, the internal capsules, and the periventricular areas but not the spinal cord, consistent with white matter disease or multifocal

Table 2. Manifestations of Neurotoxic Effects of Acyclovir^{3, 4, 8-34} and Valacyclovir^{35,36} in 45 Patients

| Characteristic | No. (and %) of Patients | |
|----------------|-------------------------|------|
| Confusion | 33 | (73) |
| Tremor | 16 | (36) |
| Hallucinations | 12 | (27) |
| Dysarthria | 12 | (27) |
| Coma | 10 | (22) |
| Agitation | 8 | (18) |
| Ataxia | 6 | (13) |
| Nystagmus | 5 | (11) |
| Seizures | 4 | (9) |
| Drowsiness | 4 | (9) |



vascular defects.⁴ The results of cerebral angiography were normal.⁴ A focal lesion was noted on computed tomography in the case reported by Blohm and others.²³ In that case magnetic resonance imaging showed a large lesion with multiple small lesions over both hemispheres in the subcortical regions.²³ These changes resolved by 9 days after discontinuation of acyclovir.

Electroencephalography, performed in 22 cases, most commonly showed diffuse slowing (15 cases),^{4,13-15,19,22,25,26,28,33} dysrhythmic activity (3 cases),^{3,13,22} triphasic waves (2 cases),^{3,26} paroxysmal delta activity (1 case),¹⁹ polyspike wave activity (2 cases),²² moderate generalized disturbances (2 cases),^{12,20} diffuse cortical alteration (1 case),³⁴ and elliptiform activity (3 cases).^{17,22} In 3 cases the results of repeat electroencephalography were normal 7 to 20 days after the acyclovir was stopped.^{13,22}

Plasma acyclovir concentration was determined in 27 cases. Trough concentrations were typically reported. The time after the last dose was not reported in all cases; when reported, this time ranged from 6 to 60 h. Plasma concentrations ranged from 1.12 to 295 $\mu\text{mol/L}$ (mean 80.8 $\mu\text{mol/L}$). In adults with normal renal function, 1-h acyclovir infusions of 10 mg/kg administered every 8 h produced mean steady-state peak plasma concentrations of 100.8 $\mu\text{mol/L}$ and mean steady-state trough concentrations of 8.4 $\mu\text{mol/L}$.¹ In 20 (74%) of the patients, plasma acyclovir concentration was less than 100 $\mu\text{mol/L}$, which suggests that plasma concentrations of the drug do not correlate with the neurotoxic effects.

Complete neurological recovery occurred in all but 3 cases. Two patients died, although their deaths were probably unrelated to the acyclovir toxicity.^{16,30} Multifocal neurological deficits persisted in one patient; these deficits were thought to be due to encephalitis or vasculitis related to varicella zoster infection.⁴ This patient was left with a right facial droop and flaccid right-sided hemiparesis.

DISCUSSION

In both cases of valacyclovir neurotoxicity reported here, the findings were compatible with the typical findings of acyclovir toxicity as presented in the literature. The patients presented to hospital within 5 days of initiation of valacyclovir therapy with confusion, ataxia, and dysarthria. In both cases, the only medication added before development of the symptoms was valacyclovir. Computed tomography results were normal, and all cultures were negative. The results of cerebrospinal fluid analysis showed elevation of protein levels in both cases and elevation of white blood cells in case 2, results consistent with those reported in the

literature. In case 1, the electroencephalography results were abnormal, suggesting drug toxicity. The patient had a history of confusion but had previously used steroids, which are known to cause central nervous system side effects. In case 2, magnetic resonance imaging of the head revealed no abnormalities. Hypertensive encephalopathy was ruled out in case 2, as the patient's blood pressure was reduced to 128–150/76–96 mm Hg within 36 h, but the neurological symptoms persisted. The normal serum concentrations of p-ANCA and c-ANCA ruled out a central nervous system exacerbation of Wegener's granulomatosis.³⁷ The ANCA's are most useful in the diagnosis of noninfectious systemic vasculitis.³⁷ These antibodies are directed against certain proteins in the cytoplasm of neutrophils.³⁸ More than 90% of patients with typical Wegener's granulomatosis and active glomerulonephritis have a positive c-ANCA titer,³⁸ and disease activity of Wegener's granulomatosis can be followed with c-ANCA.³⁷

The symptoms resolved within 72 h and both patients were discharged following a return to baseline level of functioning. Valacyclovir was the most likely cause of the neurological toxicity.

Most patients with acyclovir-induced neurotoxicity described in the literature were receiving the drug for dermatological herpes zoster. Acyclovir neurotoxicity can be difficult to distinguish from herpes zoster encephalitis. With the latter condition the average time between dermatological and neurological symptoms is approximately 1 week.³ Acyclovir is usually given within 2 days of the onset of rash, and the onset of neurological symptoms is usually within 5 days. This poses a diagnostic dilemma for the clinician, given that herpes zoster encephalitis and acyclovir neurotoxicity share disturbance of mentation as the most frequent manifestation. In one-third of cases of herpes zoster encephalitis, the patient presents with signs of meningeal inflammation (headache, nuchal rigidity, and cranial neuropathy).³ Acyclovir neurotoxicity can be distinguished from viral encephalitis by the absence of fever, headache, and focal neurological deficits, lack of lateralization of electroencephalographic findings, and normal results of cerebrospinal fluid analysis and computed tomography.⁴ Inflammatory changes in the cerebrospinal fluid may be more useful indicators, in that acyclovir neurotoxicity is rarely associated with significant pleocytosis.³ Because pleocytosis is not universal among patients with herpes zoster encephalitis (occurring in 87%), only the presence of inflammatory cells can help distinguish herpes zoster encephalitis from acyclovir neurotoxicity.³ The

2 cases presented here are consistent with the reported presentation and resolution of acyclovir neurotoxicity.

Pharmacists should be aware of the neurotoxic potential of acyclovir and valacyclovir and the importance of dosage adjustment in patients with renal dysfunction.

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