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CASE REPORT

# Severe mental disorders following anti-retroviral treatment in a patient on peritoneal dialysis: A case report and literature review

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**Author contributions:** Yang Y performed the investigation and provided resources for the case care and report; Xia M, Ying GH collected the patient's clinical data; He XL analyzed data; He QE wrote the first draft of the article; Chen JH and Yang Y reviewed and edited the article for important intellectual content.

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## Abstract

*BACKGROUND*

Antiviral drugs are widely used in populations with viral infection caused by immunologic inadequacy. Because these drugs are mainly metabolized by the kidneys, patients with renal failure undergoing renal replacement therapy are prone to drug adverse effects and poisoning. Severe neurotoxicity caused by antiviral drugs is a rare but life-threatening complication.

*CASE SUMMARY*

This study reported one male patient on peritoneal dialysis who suffered from severe mental disorders after receiving an overdose of acyclovir and valacyclovir for the treatment of herpes zoster. The literature review suggested that hemodialysis is better than peritoneal dialysis to clear acyclovir from the circulation. The patient died after his consciousness deteriorated despite peritoneal dialysis and continuous blood purification.

*CONCLUSION*

This case emphasizes cautiousness when using anti-retroviral drugs in patients with uremia. Hemodialysis is optimal method to remove the drugs.

**Key words:** Chronic renal failure; Peritoneal dialysis; Acyclovir; Valacyclovir; Neurotoxicity; Herpes zoster; Case report

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**Core tip:** A patient on peritoneal dialysis who received an overdose of anti-virals showed severe mental disorders. Peritoneal dialysis and continuous renal replacement therapy did not improve the symptoms. Hemodialysis is recommended to remove excess drugs.

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## INTRODUCTION

Herpes zoster occurs upon reactivation of varicella zoster virus and is characterized by pain and blistering skin eruption with dermatomal distribution[1-4]. The occurrence of herpes zoster increases with decline in T-cell-mediated immunity, which may occur with age or immunosuppression[1-4]. The rash typically resolves in 2-4 wk, but nerve pain may continue for months to years[1,3]. Beside pain management, anti-retroviral drugs can be used in patients without response to topical anti-retroviral, age ≥ 50 years, moderate to severe pain, severe rash, and/or non-truncal involvement[2,4]. The common drugs include valacyclovir, acyclovir, foscarnet, and bruvudin[2]. Compared with acyclovir, valacyclovir has advantages such as better oral effectiveness and tolerance, high water solubility, and less adverse reactions. Valacyclovir rapidly transforms into acyclovir after entering the body. Its common side effects include nausea, vomiting, and discomfort[5].

One possible, albeit rare, side effect of anti-retroviral drugs is central nervous system toxicity, which has been described since the 1980s[6-9]. The symptoms in patients with previously normal brain function may include visual hallucinations, death delusion, tremor, and coma, with onset of 24-72 h after starting acyclovir[8]. The symptoms are possibly due to a metabolite of acyclovir that is found at high levels in the cerebrospinal fluid of patients with neuropsychiatric symptoms[10]. Since 90% of acyclovir is cleared by the kidneys, patients with chronic kidney disease have increased serum half-life of acyclovir[11]. Most patients with neuropsychiatric disorders under acyclovir treatment have renal function impairment[10].

We present one patient on peritoneal dialysis who suffered from severe mental disorders after taking an overdose of antiviral drugs for herpes zoster. The patient died after his consciousness did not improve after peritoneal dialysis and continuous blood purification.

## CASE PRESENTATION

### *Chief complaints*

A 65-year-old man on peritoneal dialysis was referred to our hospital in July 2018 with complaints of blisters on the left frontal area with pain, and unstable walking and hallucinations.

### *History of present illness*

The patient felt severe pain in the left frontal face, with blisters for 6 d, and was diagnosed with herpes zoster. He was given antiviral treatment with intravenous acyclovir 0.5 g qd and dexamethasone 5 mg qd to relieve pain (continuous treatment for 3 d). The dermatologist prescribed oral valacyclovir 0.3 g bid after 3 d. Nonetheless, the patient misunderstood the recommendation, and received acyclovir and valacyclovir simultaneously. After 2 d of treatment, the local facial pain was relieved, and the blisters became stable, but he became with unstable walking and involuntary shaking of the limbs, accompanied by hallucinations (irregular fluttering of objects when the eyes were closed), irritability, and lethargy. He denied fever, loss of consciousness, epilepsy, suicidal or homicidal ideation, and a sudden stop of dialysis. Before onset, the patient had mild temperament and took care of himself in the daily life.

### *History of past illness*

The patient had a history of hypertension for more than 10 years, under control using

nifedipine controlled release tablets 30 mg bid and valsartan 80 mg bid.

He was diagnosed with idiopathic chronic renal failure (stage 5). He had been receiving peritoneal dialysis treatment for 3 years. He was anuretic at admission using peritoneal dialysis solution with 2.5% calcium glucose 2000 mL × 4 bags, continuous ambulatory peritoneal dialysis (CAPD), with an ultrafiltration of 1200 mL/d.

### Personal and family history

The patient denied any personal or family history of diseases.

### Physical examination upon admission

On admission, the body temperature 37.2 °C, pulse 107 bpm, breathing 20/min, blood pressure 175/108 mmHg, intermittent mild disturbance of consciousness, and with visible scattered red blister rash in the left eyelid and left forehead, which was protruded and tender, but otherwise with normal superficial lymph nodes and cardiopulmonary examinations. Nervous system examination showed negative Pap's sign but normal muscle tension in limbs.

### Laboratory examinations

The laboratory examinations showed: White blood cells 7.8 × $10^9$/L, hemoglobin 86 g/L, albumin 28 g/L, creatinine 1146 μmol/L, urea nitrogen 21.6 mmol/L, uric acid 277 μmol/L, potassium 4.2 mmol/L, sodium 145 mmol/ L, chlorine 100 mmol/L, $PO_2$ 43 mmHg, $TCO_2$ 24 mmol/L, glucose 4.7 mmol/L, and iPTH 313 pg/mL. Dialysis adequacy: KT/V = 1.64 (1 mo ago), Ccr= 41.4 L/wk. The electrocardiogram showed normal sinus rhythm. The lumbar puncture showed: Cerebrospinal fluid pressure 155 $mmH_2O$, proteins 542 mg/L, glucose 4.64 mmol/L, chlorine 121.7 mmol/L (no abnormality), and negative bacteria and tuberculosis.

### Imaging examinations

There were no obvious abnormalities in head and chest computed tomography (CT) as well as head magnetic resonance imaging (MRI).

## FINAL DIAGNOSIS

Based on the laboratory test results and imaging examinations, the differential diagnoses of cerebrovascular accidents, viral encephalitis and uremia encephalopathy were ruled out. Since he had a clear history of overdose of antiviral drugs 6 days prior to the onset of the psychiatric symptoms, the patient was finally diagnosed as mental disorders caused by antiviral drugs.

## TREATMENT

Immediately after admission, valacyclovir was discontinued, the peritoneal fluid was increased to 5 bags/d, 2000 mL per bag, and CAPD mode, and the blood pressure was dropped to around 150-160/90 mmHg after antihypertensive treatment with Adalat 30 mg bid, valsartan 80 mg bid and perindopril 8 mg qd. After 2 d of treatment, the involuntary limb shaking was not relieved and the disturbance of consciousness progressively aggravated (drowsiness-delirium-coma). On the third day after admission (July 31, 2018), the patient's respiratory failure worsened, blood gas analysis showed: pH 7.18, $PO_2$ 81 mmHg (oxygen), and $PaCO_2$ 77 mmHg, revealing carbon dioxide retention and type 2 respiratory failure. After intubation and respiratory support, the patient was transferred to the intensive care unit (ICU) on the fourth day after admission. In the ICU, peritoneal dialysis was discontinued and continuous renal replacement therapy (CRRT) was started.

## OUTCOME AND FOLLOW-UP

Though given positive rescue treatment, the patient’s consciousness was not improved. The patient died 6 d after admission.

## DISCUSSION

Herpes zoster usually develops in patients with compromised immune function. Patients on dialysis are at high risk of Herpes zoster. Both valacyclovir and acyclovir

are considered to have strong inhibitory effects on types 1 and 2 herpes virus and varicella herpes virus[12]. Valacyclovir is a precursor of acyclovir, which is converted to acyclovir by the liver. Compared with acyclovir, it has the advantages of higher absorption rate, more better pharmacokinetics and pharmacodynamics, and lower frequency of use[5].

The neurotoxicity of acyclovir was reported as early as the 1980s[6-9]. The clinical manifestations include consciousness disorders and hallucinations, fantasy, insomnia, photoallergies, dysarthria, paresthesia, and coma[13-17]. If uremia patients develop neuropsychiatric symptoms during anti-retroviral treatment, it is especially important to promptly identify and discontinue the suspicious drugs. Clinicians tend to overlook drug-induced neuropsychiatric disorders. The patient had a history of excessive use of antiviral drugs and showed obvious neuropsychiatric symptoms, despite normal head CT and MRI, and lumbar puncture and cerebrospinal fluid examination. In the present report, the patient had limb shaking, visual hallucinations, and severe disturbances of consciousness, and these symptoms progressively aggravated, which is very rare.

Valacyclovir-associated neurotoxicity usually occurs within 48-72 h of treatment start, and the symptoms can be gradually relieved after the drug is discontinued for 4-14 d (Table 1). For the patient in the present study, the time of onset and duration of symptoms were similar to those reported in literature[14,16-25] (Table 1).

Since acyclovir is mainly cleared by the kidneys, it is a consensus to reduce its dose in patients with renal failure[25]. The dose is mainly determined by a combination of factors such as different methods of dialysis, residual renal function, hydration, and age. The dose of drug used in many cases of neurotoxicity is often greater than the recommended dose[11,24]. It is generally believed that a concentration of acyclovir of 2.5-4.5 μg/mL[26] or a concentration of its main metabolite, carboxymethoxy methylguanine, above 10.8 μmol/L[10] in plasma leads to neurotoxicity. Nevertheless, there is still no consensus on the specific numerical reference range of therapeutic and toxic doses of such drugs, and it is difficult to measure the drug levels in clinical practice.

In the case reported here, increasing the dose of peritoneal dialysis and retention time still could not alleviate the clinical symptoms. Acyclovir and valacyclovir are both soluble and low-protein-bound drugs. In terms of the effectiveness of valacyclovir, a single hemodialysis for 6 h can remove about 60% of the drug, while it is considered to have poor clearance by peritoneal dialysis. On the other hand, case reports suggested that peritoneal dialysis with continuous perfusion of super-dose peritoneal dialysis solution can promote the clearance of valacyclovir[13,21,24,27]. Studies have shown that in patients with normal renal function, 89% of valacyclovir can be cleared from the urine in the form of acyclovir after 2.5-3.3 h, while the half-life of the drug is extended to 14-20 h in patients receiving CAPD for uremia (4 × 2 L exchange dose), and only 5.27 mL/min (0.355 L/h/1.73 $m^2$) can be cleared by peritoneal dialysis[21,27]. After a 6-h hemodialysis, the hemodialysis clearance rate of acyclovir is up to 113 mL/min and the plasma drug concentration can be reduced by 61.6%. Therefore, hemodialysis is at least 20 times better than peritoneal dialysis in terms of clearance effect. Based on the large differences in clearance rates between the two dialysis methods, it is suggested to switch peritoneal dialysis to hemodialysis to increase the effect of drug clearance[20,24,28]. Nevertheless, when neurotoxicity occurs, the expected improvement of neurotoxicity by hemodialysis may be delayed, even for a few days. Kageyama *et al*[29] reported a 75-year-old hemodialysis male who presented with hallucinations, dysarthria, and psychotic symptoms after intravenous acyclovir with reduced dose, which further indicates that the dose adjustment of these drugs is difficult and needs to be comprehensively individualized. CRRT has a good effect on clearing drugs with middle-and-large molecular weight or high protein binding rate. Meanwhile, valacyclovir and acyclovir are soluble and have a low protein binding rate, but there is a lack of literature on the efficacy of CRRT in clearing acyclovir and valacyclovir.

## CONCLUSION

In summary, clinicians need to be extra cautious when applying antiviral drugs in patients with renal failure. They need to be alert to the possible serious neuropsychiatric symptoms, need to adjust dose according to the level of renal function, pay attention to treatment course and hydration, be fully aware of the possible neurotoxicity caused by these drugs, and be aware of the good prognosis after early identification and active intervention. In the meantime, since the clearance rate of these drugs is low when using peritoneal dialysis, these patients should be

**Table 1 The reported cases of acyclovir/valacyclovir neurotoxicity in the literature**

| Author | Year of publication | Patient sex/age | Stage of CKD | Renal replacement manner | Dosage (mg/d) | Duration of antiviral treatment | Concomitant medication | Neuropsychiatric symptoms | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Pipili *et al*[18] | 2013 | Female/72 | ESRD | PD | Valacyclovir tablets 3 g daily for 3 d | 3 d | Nifedipine, irbesartan, cinacalcet, atorvastatin, alfacalcidol | Confusion and visual hallucinations | 3 d, restored after PD 6 × 2 L per day |
| Chaudhari *et al*[16] | 2014 | Male/66 | ESRD | PD | Oral valacyclovir 1000 mg daily for 7 d | 7 d | Simvastatin, metoprolol, sevelamer, furosemide, and glimepiride | Hallucination, insomnia, and photosensitivity | 7 d, improved after regular regimen and hydration |
| Asahi *et al*[17] | 2009 | Female/78 | Without previous renal failure | NO | Valacyclovir 3000 mg/d | 6 d | Not mentioned | Unconsciousness | 5 d, recovered 14 d later |
| Asahi *et al*[17] | 2009 | Male/73 | ESRD | Hemodialysis | Valacyclovir 3000 mg/d | 2 d | Not mentioned | Confusion, hallucination | 2 d, completely recovered 3 d later |
| Singh *et al*[19] | 2014 | Female/58 | ESRD | HD | Valacyclovir 500 mg/d | 2 d | Not mentioned | Altered sensorium, irritability, drowsiness, confusion | 2 d, completely recovered 5 d later |
| Kambhampati *et al*[20] | 2011 | Female/49 | ESRD | Maintenance hemodialysis | Valacyclovir 1000 mg three times a day | 2 d | Not mentioned | Disoriented, confused, agitated, hallucinating, delirious, incoherent | 1 d, 4000 mg, completely recovered after second session of hemodialysis |
| Prasad *et al*[14] | 2017 | Female/57 | ESRD | PD | 1000mg three times per day of valacyclovir | 3 d | Not mentioned | Confusion and altered sensorium | 1 day, completely recovered 24h later |
| Izzedine *et al*[21] | 2001 | Female/60 | ESRD | PD | Valacyclovir 500 mg daily | Reduced 500 mg of valacyclovir every 2 d | Not mentioned | Disorientated with ocular and auditory hallucinations and loss of decorum without torpor or coma. | 3 d, recovered 48 h later |
| Strumia *et al*[22] | 2004 | Male/81 | ESRD | Hemodialysis | Oral valacyclovir 1000 mg every 8 h then intravenous acyclovir in full dosage | 3 d | Not mentioned | Visual hallucination, confusion and disorientation | 3 daysd completely recovered 6 d later |
| Linssen-Schuurmans *et al*[23] | 1998 | Male/58 | CKD | Intermittent hemodialysis twice a week | Valacyclovir 3 g/d | 2 d | Not mentioned | Dizziness, hallucinations, loss of decorum, disoriented, slurred speech | 1 d, complete recovery |
| Takayanagi *et al*[24] | 2010 | Male/67 | ESRD | PD | Valacyclovir, 1 g/d | 5 d | Not mentioned | Hallucinations | 7 d, complete recovery |
| Sadjadi *et al*[25] | 2018 | Male/80 | ESRD | PD | Acyclovir 5 mg/kg intravenously, followed by oral acyclobir 400 mg/d | 3 d | Not mentioned | Confusion, delusion, disorientation, restlessness, visual hallucinations, seizures | 2 d, complete recovery |

CKD: Chronic kidney disease; ESRD: End-stage renal disease; PD: Peritoneal dialysis.

switched to hemodialysis.

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