# Are Neuropsychiatric Symptoms, Meningeal Irritation Signs, and Cerebellar Signs Clinical Manifestations of Acyclovir Toxicity?

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***Background and Objective:*** *Acyclovir is primarily cleared by the kidneys. Therefore, renal adjusted dosing is required for patients with renal impairment to prevent drug toxicity. This study aimed to demonstrate the clinical manifestations and treatment in case series of acyclovir toxicity.*
***Material and Method:*** *We retrospectively reviewed 6 patients who were diagnosed acyclovir toxicity between January 1, 2005 and January 31, 2016 at Khon Kaen University's Srinagarind Hospital.*
***Results:*** *All 6 patients were diagnosed with herpes zoster infection and renal dysfunction. There were four end-stage renal disease (ESRD) patients and two chronic kidney disease (CKD) patients. The neuropsychiatric symptoms occurred within approximately 1-2 days after acyclovir was prescribed in ESRD patients and in 3 days in CKD patients. The symptoms were lethargy, drowsiness, visual hallucinations, dysarthria, mutism, seizures, myoclonus, and weakness. Additionally, meningeal irritation and cerebellar signs were observed upon physical examination. In severe cases, the patients suffered from respiratory failure. When acyclovir toxicity was suspected, acyclovir use was discontinued in all patients and emergency hemodialysis (HD) was performed in ESRD patients. All patients completely recovered consciousness after the second session.*
***Conclusion:*** *Neuropsychiatric symptoms, meningeal irritation, and cerebellar signs may appear in cases of acyclovir toxicity. Clinical improvement after hemodialysis and discontinuation of acyclovir are key indicators leading to the diagnosis of acyclovir toxicity, and therapy should consist of two consecutive daily HD sessions.*

***Keywords:*** *Acyclovir, Toxicity, Overdose*

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Herpes zoster is a common infection, and acyclovir is widely used in its treatment[1]. Acyclovir and its main metabolite, 9-carboxy methoxy methylguanine (CMMG), are mostly removed through renal excretion. Therefore, dosage of acyclovir must be adjusted in patients with renal impairment[2]. The accumulation of acyclovir and metabolite can cause toxicity, which usually manifests as neuropsychiatric symptoms in patients suffering from acute kidney injury. However, herpes zoster encephalitis, a serious complication of herpes zoster infection, could also present as neuropsychiatric symptoms similar to those that appear in cases of acyclovir toxicity. Differential diagnosis of herpes encephalitis and acyclovir toxicity is, thus, critical in clinical practice. Strategies to help differentiate between the two conditions include the careful examination of clinical information, measuring serum acyclovir or CMMG levels, brain imaging, lumbar puncture (LP), and electroencephalogram (EEG)[3,4]. There have been many case reports of acyclovir neurotoxicity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD)[4-10]. We demonstrated the clinical presentations and management of acyclovir toxicity in a case series of patients that presented with neuropsychiatric disorders.

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## Material and Method

We retrospectively reviewed six patients who were diagnosed with acyclovir toxicity between January 1, 2005 and January 31, 2016 in Srinagarind Hospital, a university hospital in Khon Kaen, Thailand. As serum acyclovir and CMMG level testing were unavailable,

acyclovir toxicity was diagnosed based on clinical symptoms and investigation for exclusion of other causes. Patient characteristics, co-morbidity, laboratory findings, presentation of neurologic symptoms, acyclovir dosage, hemodialysis treatment, and clinical outcomes were recorded. This study was approved by the Khon Kaen University Ethics committee in human research (HE591561).

**Results**

This study found six patients who were diagnosed with acyclovir toxicity (four men and two women). Two of these patients were on continuous ambulotory peritoneal dialysis (CAPD), one was receiving hemodialysis (HD) twice weekly, and three were CKD patients not undergoing dialysis. The age range was 56 - 82 years. All of the patients had herpes-zoster infections and received unadjusted doses of acyclovir for treatment. The clinical manifestations, drug dosages, co-morbidity, investigation, treatment, and outcomes are summarized in Table 1.

After the prescription acyclovir, onset of neuropsychiatric symptoms in ESRD patients developed earlier than in CKD patients (1-2 days and 3-4 days, respectively). The neuropsychiatric symptoms included drowsiness, lethargy, confusion, mutism, visual hallucinations, lethargy, and diffuse motor weakness. Some patients had a history of seizures, myoclonus, signs of meningeal irritation, and positive of cerebellar signs. Two ESRD patients experienced acute respiratory failure and required a mechanical ventilator because of CNS suppression. Finally, one patient had aspirated pneumonia.

Computer tomography (CT) of the brain was performed in five of six patients, and the results could not account for the symptoms. Lumbar puncture was performed in three of six patients, and the results were acellular profiles in two specimens and a traumatic profile in one specimen.

Acyclovir-induced neuropsychiatric disorder was suspected in all patients. Therefore, acyclovir use was discontinued. We performed emergency hemodialysis in four ESRD patients (three dialysis-dependent [two CAPD and performed one HD] and one ESRD non-dialysis). After the first session of HD, the clinical symptoms had improved dramatically, and patients were prescribed HD for two consecutive days. Subsequently, the patients fully recovered from their clinical symptoms. In CKD patients, their clinical symptoms slowly improved over three to four days after discontinuation of acyclovir (without HD).

**Discussion**

Acyclovir is routinely used for treatment of herpes-zoster infection and is mainly excreted by the kidneys. Therefore, a renal-adjusted dose is required to prevent drug toxicity, which usually presents as nephrotoxicity and neurological disorders.[1] In ESRD patients, loading and maintenance of acyclovir are likely to be 400 mg and 200 mg, respectively, twice daily. The patients in this study received dosages approximately 4-10 times greater than the proper dosage regimen for their renal function. Therefore, it is critical that the physicians prescribe renal adjusted doses of acyclovir. Acyclovir toxicity can be diagnosed by testing blood and CSF acyclovir levels and CMMG levels[11] . However, recent data have shown a lack of association between acyclovir levels and clinical symptoms[12], and these tests are not widely available. It is difficult to distinguish between herpes encephalitis and acyclovir-induced neurotoxicity in a clinical setting. However, the absence of neurological deficit, acellular CSF, normal brain CT, normal EEG[3], worsening of clinical symptoms within 24-48 hours of taking acyclovir[4], and improvement of clinical symptoms after HD have been suggested to be compatible with acyclovir toxicity[6]. In this study, serum acyclovir and CMMG tests were not available. Our patients were investigated in order to exclude other causes, and their clinical symptoms improved after HD and discontinuation of acyclovir. Therefore, acyclovir toxicity was the most likely diagnosis. In CKD patients, acyclovir usage was discontinued and clinical symptoms subsequently improved. This is indirect evidence to support acyclovir toxicity rather than herpes encephalitis.

According to these results, acyclovir toxicity should be investigated in patients who present with neuropsychiatric symptoms similar to those detailed in previously reports[4-11]. Although, meningeal irritation and cerebellar signs were not mentioned in these prior reports, our finding suggests that they may be signs of acyclovir toxicity.

Acyclovir has a low volume distribution (0.69 L/kg) and exhibits low protein binding (15%)[2]. Therefore, HD is a therapeutic option for the rapid clearance of acyclovir and metabolite. Previous studies have shown complete clinical reversibility in acyclovir toxicity[4-11] after a second or third session of HD, which is compatible with our findings in this report.

**Conclusion**

Acyclovir toxicity should be investigated in CKD patients who have received unadjusted acyclovir

**Table 1.** The clinical manifestations, clinical course and treatment outcome in acyclovir toxicity patients

| Characteristics | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Year | January 2011 | May 2011 | March 2015 | May 2015 | October 2015 | January 2016 |
| Age (years) | 84 | 68 | 66 | 73 | 56 | 80 |
| Gender | Female | Male | Female | Male | Male | Male |
| Comorbidity | ESRD without dialysis, T2DM and HT | CKD stage 4, T2DM, HT and DLP | CKD stage 3b, HT and old CVA | ERSD and HT on conventional HD x2/week | ESRD on CAPD 1.5% 2Lx4 exchanges, DVD with stent, HT and DLP | ESRD on CAPD 1.5% 2Lx4 exchanges, T2DM, HT and MDS |
| Skin diseases | Herpes zoster on T12 dermatome | Disseminated herpes zoster | Herpes zoster; unspecified dermatome | Herpes zoster on C5 dermatome | Herpes zoster on L1 dermatome | Herpes zoster on T4 dermatome |
| Acyclovir doses | 1000 mg/day | 4000 mg/day | 4000 mg/day | 1600 mg/day | 4000 mg/day | 4000 mg/day |
| Onset after administration | 2 days | 4 days | 3 days | 1 day | 2 days | 1 days |
| Clinical manifestations | Confusion, lethargy visual hallucination drowsiness myoclonus and diffuse motor weakness | Confusion, ataxia, nystagmus, present of cerebellar signs: Rhomberg positive & impair Tandem gait | Ataxia, diffuse motor weakness, present of cerebellar signs: Rhomberg positive, impaired Tandem gait, dysdiadochokinesia & dysmetria | Drowsiness, mutism, diffuse motor weakness seizures and meningeal irritation | Confusion, drowsiness, lethargy, dysarthria and myoclonus | Drowsiness, mutism, lethargy |
| Complications | Respiratory failure with mechanical ventilator | None | None | Respiratory failure with mechanical ventilator | None | Aspirated pneumonia |
| CT brain | Brain atrophy | Not performed | Lacunar infarction at internal capsule | Generalized brain edema | Multiple area of lacunar infarction | Old cerebral infarction |
| EEG | No epileptic discharge | Not performed | Not performed | Epileptic discharges were found | Not performed | Not performed |
| CSF profile | Normal | Not performed | Not performed | Traumatic profile | Normal | Not performed |
| CSF PCR for Herpes | Not performed | Not performed | Not performed | Negative | Negative | Not performed |
| Treatment and HD sessions/time (hours) | 2 sessions on consecutive days<br>1st: 3 hours<br>2nd: 3 hours | HD was not performed. After discontinuation of acyclovir, 4 days later: improvement of clinical symptoms | HD was not performed. After discontinuation of acyclovir, 4 days later: improvement of clinical symptoms | 2 sessions on consecutive days<br>1st: 3 hours<br>2nd: 4 hours | 2 HD sessions on consecutive days<br>1st: 3 hours<br>2nd: 4 hours | 2 HD sessions on consecutive days<br>1st: 3 hours<br>2nd: 4 hours |
| Clinical outcomes | Full recovery Off ET tube after 2nd HD | Full recovery | Full recovery, but complicated by aspirated pneumonia | Full recovery Off ET tube after 2nd HD session | Full recovery | Full recovery, but complicated by aspirated pneumonia |

CAPD = continuous ambulatory peritoneal dialysis; CSF = cerebral spinal fluid; CVA = cerebrovascular accident; DLD = dyslipidemia; DVD = double vessel disease; EEG = electroencephalogram; ET tube = endotracheal tube; MDS = myelodysplastic syndrome; HD = hemodialysis; HT = hypertension; T2DM = diabetes mellitus type 2

doses and present with neuropsychiatric symptoms or meningeal irritation and cerebellar signs. However, other causes should first be excluded. If the diagnosis is suspected acyclovir toxicity in ESRD patients, patients should immediately discontinue acyclovir usage and should undergo emergency hemodialysis. Two consecutive daily sessions of HD in is adequate treatment for acyclovir toxicity.

**What is already known on this topic?**

Acyclovir toxicity and herpes encephalopathy are difficult to distinguish with regard to their neuropsychiatric presentation. Neurological examination, imaging, CSF fluid analysis, serum CMMG levels, and clinical concerns are helpful methods of diagnosis.

**What this study adds?**

Neuropsychiatric manifestations occur approximately 24-48 hours after acyclovir prescription. This study found that meningeal irritation signs and cerebellar signs may occur in patients with acyclovir toxicity. However, other conditions should be excluded in patients with abnormal neurological examination results. Additionally, if the patients show clinical improvement after discontinuation of acyclovir therapy and hemodialysis, acyclovir toxicity is the most likely diagnosis. In that case, a treatment strategy consisting of two consecutive daily hemodialysis sessions is effective.

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**Potential conflicts of interest**

None.

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# *อาการความผิดปกติทางจิตประสาท อาการระคายเคืองเยื่อหุ้มสมองและอาการความผิดปกติของสมองน้อยเป็นอาการแสดงถึงภาวะเป็นพิษจากยาอะไซโคลเวียร์ได้หรือไม่*

***พรรณธิพา ต้นสวรรค์, กิตติ์รวี กฤษฎิ์เมธาภาคย์, กรรณิการ์ คงบุญเกียรติ, สุดา วรรณประสาท***

***ภูมิหลังและวัตถุประสงค์:*** *ไตเป็นอวัยวะหลักในการขับยาอะไซโคลเวียร์ ดังนั้นการใช้ยาในผู้ป่วยโรคไตเรื้อรัง จึงต้องปรับขนาดยาตามการทำงานของไต เพื่อหลีกเลี่ยงการเกิดพิษจากยา การศึกษานี้ต้องการนำเสนอกรณีศึกษา ผู้ป่วยที่ได้รับการวินิจฉัยพิษจากยาอะไซโคลเวียร์*

***วัสดุและวิธีการ:*** *ศึกษาแบบย้อนหลังโดยการรวบรวมผู้ป่วยที่ได้รับการวินิจฉัยพิษจากยาอะไซโคลเวียร์ระหว่างวันที่ 1 มกราคม พ.ศ. 2548 และวันที่ 31 มกราคม พ.ศ. 2559 ที่โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น*

***ผลการศึกษา:*** *ผู้ป่วยทั้งหมด 6 รายได้รับการวินิจฉัยโรคงูสวัดและโรคไต โดยมีผู้ป่วย 4 รายเป็นโรคไตเรื้อรัง ระยะสุดท้ายและ 2 รายเป็นโรคไตเรื้อรังพบว่าผู้ป่วยโรคไตเรื้อรังระยะสุดท้ายเกิดอาการความผิดปกติ ทางจิตประสาทประมาณ 1-2 วันหลังได้รับยา ในขณะที่ผู้ป่วยโรคไตเรื้อรังเกิดขึ้นประมาณ 3 วัน อาการที่พบได้แก่ เชื่องช้า ซึม เห็นภาพหลอน พูดไม่ชัด ไม่ยอมพูด ชัก การเคลื่อนไหวผิดปกติแบบกระตุกและอาการอ่อนแรง นอกจากนี้จากการตรวจร่างกายในผู้ป่วยที่วินิจฉัยภาวะเป็นพิษจากยาอะไซโคลเวียร์ ยังพบสามารถอาการระคายเคืองเยื่อหุ้มสมอง และอาการแสดงของสมองน้อยผิดปกติ หากผู้ป่วยมีอาการรุนแรงสามารถเกิดระบบหายใจล้มเหลวได้ เมื่อสงสัยภาวะเป็นพิษจากยาอะไซโคลเวียร์ ผู้ป่วยทุกคนได้รับการรักษาโดยให้หยุดยาทันทีและกรณีผู้ป่วย โรคไตเรื้อรังระยะสุดท้ายได้รักษาเพิ่มโดยการฟอกเลือดด้วยเครื่องไตเทียม ซึ่งผู้ป่วยกลุ่มนี้อาการหายเป็นปกติ หลังการฟอกเลือดจำนวน 2 ครั้ง*

***สรุป:*** *อาการทางจิตประสาท อาการระคายเคืองเยื่อหุ้มสมอง และอาการแสดงของสมองน้อยผิดปกติสามารถพบได้ ในภาวะเป็นพิษจากยาอะไซโคลเวียร์ โดยหากอาการเหล่านี้ดีขึ้นภายหลังการการหยุดยาและการฟอกเลือด เป็นสิ่งที่ช่วยยืนยันการวินิจฉัย พบว่าการฟอกเลือดวันละ 1 ครั้ง 2 วันติดกันเพียงพอในการรักษา*