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VALACYCLOVIR INDUCED NEUROTOXICITY, WITH THERAPEUTIC DRUG MONITORING, IN A HOSPITAL-BASED SETTING IN THE NETHERLANDS

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ABSTRACT

Background: Valacyclovir-induced neurotoxicity is a rare side effect. The aim of this study was to perform a retrospective analysis of patients with valacyclovir-induced neurotoxicity and establish valacyclovir plasma concentrations in a tertiary hospital between January 2018 and November 2022.

Case descriptions: In total 208 patients were identified with measured acyclovir concentrations, and the electronic health records of these patients were analysed. Based on the in- and exclusion criteria, 4 patents were identified in whom high plasma concentrations were linked to neurotoxicity. The first patient experienced balance and coordination problems, visual hallucinations, speaking difficulties and headaches. The second patient experienced a progressive decline of consciousness, resulting in coma. The third patient also experienced reduced consciousness and was found unconscious on the floor during the night. The fourth patient experienced vertigo after administration of acyclovir.

Conclusion: Based on this study, neurotoxicity appears to be an underreported adverse effect of valacyclovir therapy in a hospital setting. This side effect may have a high impact on individuals as well as on the duration of hospitalization. In order to exclude valacyclovir as the cause, clinicians should consider requesting an acyclovir plasma concentration as standard hospital-based intervention whenever a patient experiences neurotoxic symptoms. Moreover, pharmacists and clinicians should be made better aware of the interaction between valacyclovir and cyclosporine and/or mycophenolic acid, in particular in elderly patients with impaired kidney function.

KEYWORDS

Valacyclovir- neurotoxicity, interactions, therapeutic drug monitoring

LEARNING POINTS

- Valaciclovir-induced neurotoxicity diagnosis is underreported.
- Accessible and frequent therapeutic drug monitoring (TDM) of valacyclovir is recommended.
- Interactions between valaciclovir and ciclosporin and/or mycophenolic acid, in particular in elderly patients with impaired kidney function, need a follow-up during hospitalization.

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INTRODUCTION

Valacyclovir is a prodrug of acyclovir and is applied in severe recurrent varicella zoster virus (VZV) infections and herpes simplex virus (HSV). In practice, valacyclovir generally shows a good profile for tolerance and safety; however, it can cause systemic adverse effects. Valacyclovir has a relevant interaction with cyclosporine[1,2]. Co-administration of both drugs enhances the chance of nephropathy, resulting in cumulation of acyclovir[1,2]. Acute renal failure is frequently described in the literature, and is caused by acyclovir precipitation and crystallization in the renal tubules[3]. Another adverse effect of acyclovir is neurotoxicity. It is hypothesized that the neuropsychiatric side effects result from an accumulation of the metabolite 9-carboxymethoxymethylguanine (CMMG) in cerebrospinal fluid[4]. Therefore, measurement of CMMG in cerebrospinal fluid could be considered in clinical practice when valacyclovir-induced neurotoxicity is suspected[5].

The aim of this study is to provide an overview of real-world outcomes and prevalence of acyclovir-induced neurotoxicity in a tertiary hospital in the Netherlands. For this study, the Medical Ethical Committee of the University Medical Centre Groningen (Groningen, The Netherlands) waived the need for written informed consent due to the retrospective nature of the study (reference 2023/056). All patients aged 16 years or older with known acyclovir plasma concentrations from January 2018 till November 2022 were included. All registrations in the electronic health records in the time period that valacyclovir was administered were examined for symptoms of neurotoxicity. Neurotoxic symptoms were related to the plasma concentration of acyclovir. Acyclovir therapeutic ranges for the treatment of HSV/VZV infections were 0.5–2.5 mg/l and 5–25 mg/l for the trough and peak concentrations, respectively. Therapeutic ranges for the treatment of herpes encephalitis were 2.0–2.5 mg/l and 20–25 mg/l for the trough and peak concentrations[6]. Concentrations above these references are considered toxic. In total 208 patients were included. There were 22 patients with neurotoxic symptoms, 4 of whom were diagnosed as valacyclovir-induced neurotoxicity in a hospital setting. These 4 patients had a score of ≥8 on the Naranjo scale, which translates to the adverse effect being probable to definite[7]. The on- and offset of the adverse effects described were linked to toxic acyclovir plasma concentrations. The other 18 patients were excluded, since the neurotoxic symptoms could not be assigned with certainty to the acyclovir therapy.

CASE DESCRIPTIONS

Case 1

A 69-year-old female with a body mass index (BMI) of 26.7 kg/m^2 was admitted to the emergency department (ED) and transferred to the department of infectious diseases with a diagnosis of VZV ophthalmicus. Three years earlier she underwent a kidney transplant for which ciclosporin and mycophenolic acid had been prescribed. After admission to the clinic, intravenous (IV) acyclovir, 10 mg/kg three times a day, was started. Two days after the switch to acyclovir the patient's laboratory results showed a peak acyclovir plasma concentration (14.1 mg/l) within the therapeutic range, and a normal serum creatinine concentration (78 µmol/l). The hospital pharmacist advised continuation of the therapy with the current dose. In the night of the 5th day of therapy, the patient experienced balance problems when walking, coordination problems, visual hallucinations when closing her eyes, speaking difficulties and a headache at the back of her head. Because a nodular cerebral infarction was suspected, the next morning a computed tomography (CT) scan of the head was performed and a blood sample was drawn. The results of the CT scan showed no evidence of recent ischemia or thrombosis. The lab results showed acute kidney failure (serum creatinine of 216 µmol/l). In *Figure 1*, the decline of the kidney function is shown. After re-evaluation of the acyclovir plasma concentration on the 2nd day, it became clear that the blood sample had been taken during the IV administration of acyclovir. The estimated acyclovir peak concentration, based on pharmacokinetic modelling of acyclovir, showed the concentration to be in the toxic range (>25 mg/l). Acyclovir was discontinued after consultation with the hospital pharmacist. The neurotoxic symptoms lasted up to 19 hours after the last infusion. In addition, there was an interaction notification for the combined use of valacyclovir and ciclosporin. However, no dose adjustments were deemed necessary because no symptoms of acute nephropathy were found at the moment that the first interaction occurred. Since renal function was monitored, it was assumed that an indication of acute kidney failure would be registered. No interaction notification was reported for simultaneous use with mycophenolic acid, which could lead to increased exposure[8].

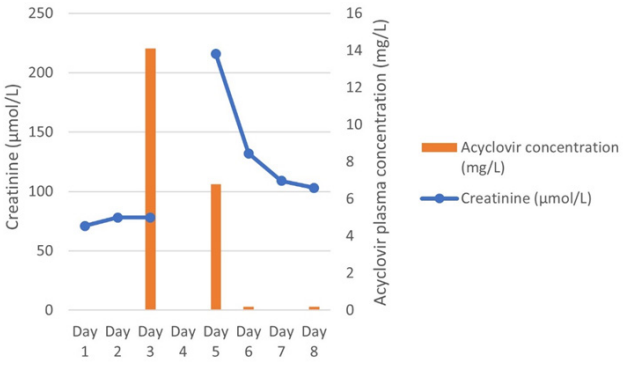

Figure 1. Relationship between acyclovir serum concentrations and serum creatinine levels in Case 1.

Case 2

A 74-year-old female with a BMI of 21.5 kg/m^2 was admitted to the ED of a peripheral hospital and transferred to a tertiary hospital where she was admitted to the intensive care unit due to respiratory insufficiency. She had been diagnosed with breast cancer with metastases in the lungs, liver and lymph nodes. Laboratory results before commencing acyclovir

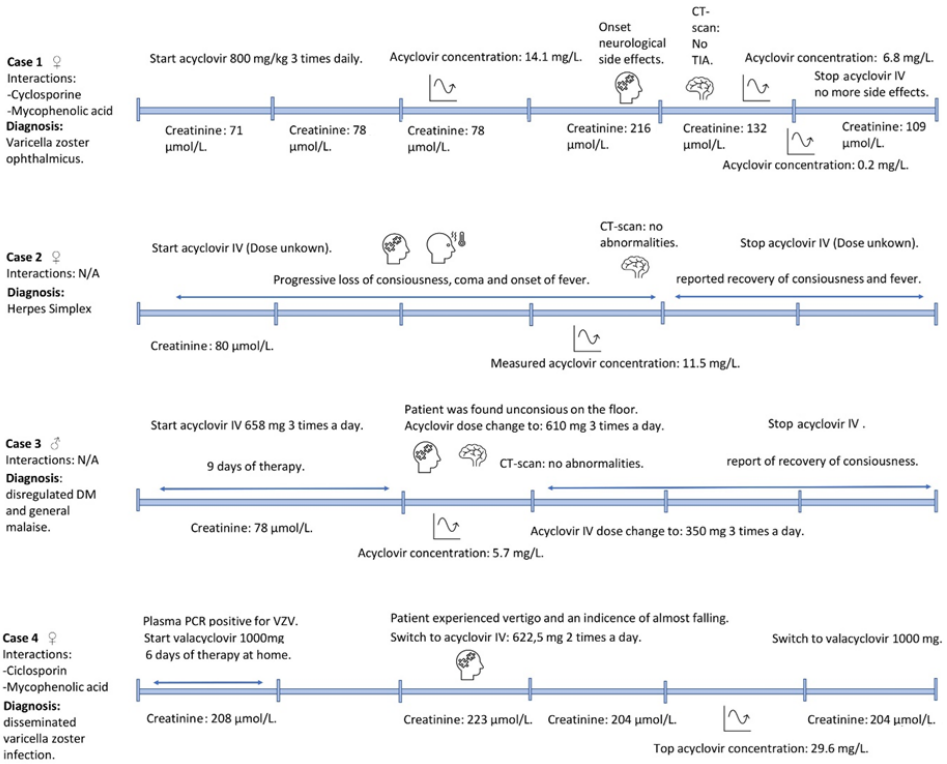

Figure 2. Schematic overview of the timelines of four cases of acyclovir-induced neurotoxicity. Every vertical bar represents 24 hours, unless otherwise indicated.

Abbreviations: TIA, transient ischemic attack; CT, computed tomography; IV, intravenous; DM, diabetes mellitus; VZV, varicella zoster virus; PCR, polymerase chain reaction.

treatment were normal (sodium serum 135 µmol/l, serum potassium 3.9 µmol/l, aspartate aminotransferase - AST, 44 U/l, alanine aminotransferase – ALT 19 U/l, serum creatinine 80 µmol/l). An acyclovir infusion was started to treat a HSV infection on her nose. After acyclovir was started, she experienced a progressive decline of consciousness, resulting in coma and the onset of fever *(Fig. 2)*. CT scans showed no structural abnormalities, and liquor collection showed no opportunistic infections or malignant cells. An acyclovir plasma concentration was determined (11.5 mg/l), but no dose advice from the clinical pharmacy was provided. Also, it was not clear whether the measured concentration was a trough, mid- or peak concentration. Acyclovir was discontinued 4 days later, after which a decrease in fever and recovery of consciousness was observed. No relevant interactions were found with her co-medication.

Case 3

A 67-year-old male with a BMI of 19.6 kg/m^2 and a history of chronic obstructive pulmonary disease, hypertension, insulin-dependent diabetes mellitus type 2 (DMII), multiple non-ST-elevation myocardial infarction (NSTEMI) and a gastric carcinoma was admitted to the ED for a herpes zoster infection on the right side of his face and transferred to the department of infectious diseases. The patient had a history of falling at home and variable consciousness that had been diagnosed as orthostasis and a trifascicular block. After a lumbar liquor puncture, the patient was also diagnosed with VZV encephalitis. Acyclovir was administered IV, 10 mg/kg three times a day, for a period of 24 days. On the 10th day of therapy, the patient experienced reduced consciousness after administration of acyclovir *(Fig. 2)*. Later the same day his consciousness was restored. The following night a nurse found him unconscious on the ground. Blood glucose was measured for suspected dysregulated DMII; however, the test results showed normal blood glucose. An acyclovir concentration was requested for suspected neurotoxicity. The trough concentration (5.7 mg/l) was found to be well above the therapeutic range. The hospital pharmacist advised to lower the dose, after which complete recovery of consciousness was seen within 24 hours. The symptoms were diagnosed as acyclovir-induced neurotoxicity. No relevant drug-drug interactions were found.

Case 4

A 36-year-old female with a BMI of 22.9 kg/m^2 and a history of kidney transplant was admitted to the nephrology department due to a disseminated VZV infection. Ciclosporin and mycophenolic acid were prescribed because of the kidney transplant. IV acyclovir was started, 10 mg/kg twice a day, since the lab results came back positive for VZV. Renal function tests showed that the acyclovir dose had been adjusted correctly (serum creatinine 208 µmol/l). Nevertheless, the patient experienced vertigo 2 days after therapy was started. In addition, a near-falling incident was reported 2 days after therapy was started *(Fig. 2)*. The vertigo remained and an acyclovir plasma concentration was requested 4 days after therapy was started. The peak concentration measured was toxic (29.6 mg/l), notwithstanding the dose adjustment for her renal function. Subsequently, IV therapy was switched to oral valacyclovir, and the dose of valacyclovir was adjusted. The day after the patient no longer experienced vertigo, and she was discharged from the hospital the same day to continue the therapy at home. No intervention was required for an interaction of ciclosporin and mycophenolic acid.

DISCUSSION

The aim of this study was to provide an overview of real-world outcomes of the prevalence of acyclovir- induced neurotoxicity in a tertiary hospital. In practice, it is difficult to relate acyclovir exposure to clinical symptoms, with confounders such as co-medication and conditions which could cause similar symptoms. Our study shows that valacyclovir-induced neurotoxicity is often a late diagnostic consideration. For future treatment with valacyclovir, we recommend frequent therapeutic drug monitoring (TDM) of valacyclovir. By implementing TDM in routine practice of valacyclovir therapy, patient care could be optimized. Furthermore, the measurement of CMMG in the cerebrospinal fluid can also be considered for inclusion in the TDM protocol of valacyclovir. This will raise awareness of the possibility of valacyclovir-induced neurotoxicity and reduce underreporting. Moreover, pharmacist and clinicians should be made better aware of the interaction between valacyclovir and ciclosporin and/or mycophenolic acid, in particular in elderly patients with impaired kidney function[8].

CONCLUSION

A standardized TDM protocol could help to exclude valacyclovir as a possible cause for symptoms of neurotoxicity in patients.

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