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Neurotoxic side effects of acyclovir: two case reports

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Abstract

Acyclovir is an antiviral drug frequently used in clinical practice. It is indicated for the treatment of infections caused by herpes simplex virus and varicella zoster virus. The drug has a good safety profile; however, severe side effects may rarely occur during therapy. These include renal failure as a major risk factor for neurotoxic side effects potentially developing within 24–48 hours of therapy initiation. The paper presents the cases of two patients developing neurotoxic side effects while treated for herpes zoster.

The aim of the authors is to highlight the potential for developing neurotoxic side effects in high-risk groups such as the elderly, patients with impaired renal function or multiple comorbidities on polypharmacy, or those using nephrotoxic drugs. Acyclovir use could lead to renal impairment and an increase in its plasma and CNS concentrations with severe neuropsychiatric side effects. The neurotoxic side effects are reversible after therapy withdrawal. Thus, in patients developing mental impairment or showing other neurological symptoms during acyclovir therapy, the patient should be promptly assessed for potential drug neurotoxicity, their therapy should be discontinued and drug elimination with forced diuresis or hemodialysis considered. Early recognition of acyclovir neurotoxic side effects can significantly improve a patient's prognosis.

CASE REPORT

INTRODUCTION

Acyclovir is an antiviral drug frequently used in clinical practice. It belongs to the key drugs included in the World Health Organization's List of Essential Medicines (Abdel-Aleem *et al.* 2012; Persaud *et al.* 2019).

Discovered in 1974, acyclovir has been used in clinical practice since the early 1980s (King, 1988; ValACYclovir Hydrochloride Monograph for Professionals, 2019).

Chemically a hypoxanthine, it is a synthetic purine nucleoside analog (1H-purin-6(9H)-one), a bicyclic aromatic compound made up of a pyrimidine ring fused to an imidazole ring inhibiting herpes virus replication (Zachary, 2020).

Acyclovir is indicated for the treatment of infections caused by herpes simplex virus (HSV) and varicella zoster virus (VZV). It is converted to acyclovir monophosphate by viral thymidine kinase (King, 1988; Smith, 2010). This nucleoside analog is subsequently phosphorylated to diphosphate to be further converted to triphosphate by cellular enzymes (Hussin *et al.* 2013; Morales-Alvarez, 2020).

Acyclovir triphosphate has been found to have higher affinity for viral DNA polymerase (HSV, VZV) than for cellular DNA polymerase and incorporates into DNA where the missing 2' and 3' carbons cause DNA chain termination. In other cases, acyclovir triphosphate competes so strongly for viral DNA polymerase that other bases cannot associate with the enzyme inactivating it (Zachary, 2020).

Acyclovir has a good safety profile; however, severe side effects may rarely occur during therapy. These include renal failure as a major risk factor for neurotoxic side effects potentially developing within 24–48 hours of therapy initiation (Cani *et al.* 2019; Ferreira *et al.* 2018; Thind & Roach 2017; Watson *et al.* 2017).

Importantly, these side effects are usually reversible and their early recognition can significantly improve a patient's prognosis. In our clinical practice, we have diagnosed, within a relatively short period of time, two cases of acyclovir-induced neurotoxicity.

Acyclovir pharmacokinetics is described in detail in Table 1 (Sadjadi *et al.* 2018).

Acyclovir can be administered either orally or intravenously for systemic therapy. Its minimal and maximal plasma concentrations with different dosing schemes and dosage forms are shown in Table 2. Acyclovir concentration in cerebrospinal fluid (CSF) is 50% of its respective plasma concentrations.

Acyclovir is eliminated from the body via the kidney with a contribution by glomerular filtration and tubular secretion (King, 1988; Richelsen *et al.* 2018).

Less than 2% of the drug is excreted in the stool with about 0.1% converted to CO_2. Approximately 10–15% of acyclovir is converted to 9-carboxymethoxymethylguanine (9-CMMG) to be again excreted via the kidney (Smith *et al.* 2010; Pedersen *et al.* 2013).

In patients with normal renal function, the biological half-life of acyclovir is relatively short, about 3 hours, extending to up to 19.5 hours in renal failure. The average half-life of acyclovir during hemodialysis is approximately 5 hours. During dialysis, plasma acyclovir concentration decreases by 60% (Sadjadi *et al.* 2018; Strumia *et al.* 2004).

Dosing in adults

The dosing schemes and intervals of administration in individual age groups according to clinical diagnosis are presented in Table 3.

Dosing in children

The dosing scheme of oral acyclovir used for the treatment or prophylaxis of HSV infections in immunocompromised patients is as follows: in neonates and infants up to 3 months of age, acyclovir doses are determined by body weight. While the dosing scheme in children older than 2 years of age is identical to that of adults,

Tab. 1. Acyclovir pharmacokinetic characteristics

Bioavailability on oral administration	10–20%
Binding to plasma protein	9–33%
Elimination	90–92% unchanged through the kidney (by glomerular filtration and tubular secretion), < 2% in the stool and < 0.1% through the lungs
Volume of distribution	0.6 L/kg
Renal clearance	248 mL/min/1.73m^2
Biological half-time	2.5–3 hrs (with normal renal function)
T_{max}	1.1 ± 0.4 hrs
C_{max}	593.7–656.5 ng/mL
AUC	2956.6–3102.5 h/ng/mL
Metabolization	<15% oxidized to 9-carboxymethoxymethylguanine by alcohol dehydrogenase and aldehyde dehydrogenase 1% 8-hydroxylated to 8-hydroxy-acyclovir by aldehyde oxidase

Tab. 2. Dose and route of administration-dependent plasma concentrations

Dose / route of administration	c_{min} (μg/mL)	c_{max} (μg/mL)
200 mg every 4 hrs, oral	0.4	0.7
400 mg every 4 hrs, oral	0.6	1.2
800 mg every 4 hrs, oral	0.9	1.8
Adults, 2.5 mg/kg, 1-hour infusion	0.5	5.1
Adults, 5 mg/kg, 1-hour infusion	0.7	9.8
Adults, 10 mg/kg, 1-hour infusion	2.3	20.7
Neonates and infants (0–3months) 10 mg/kg parenterally (1 hour) every 8 hrs	2.3	13.8
15 mg/ kg every 8 hrs	3.2	18.8

Tab. 3. Indications and dosing schemes during acyclovir therapy (SPC Aciclovir Olikla, 2020; SPC Herpesin 400, 2020)

Indication	Dose	
Treatment of HSV infection		
Mucocutaneous HSV infection in immunocompetent adults	200 mg 5 times a day orally (every 4 hrs while skipping the night-time dose)	5 days (can be extended)
HSV infection in immunocompromised patients or those with altered absorption	400 mg 5 times a day orally (every 4 hrs while skipping the night-time dose) or intravenous therapy	5 days (can be extended)
Herpes simplex encephalitis	10 mg/kg every 8 hrs	14 days (can be extended)
HSV infection prophylaxis		
HSV mucocutaneous infection in immunocompetent adults	200 mg every 6 hrs orally or 400 mg every 12 hrs orally	6–12 months
HSV infection in immunocompromised patients	200 mg every 6 hrs orally	If increased risk of infection
HSV infection in severely immunocompromised patients or those with altered absorption	400 mg every 6 hrs orally/parenteral therapy	If increased risk of infection
Treatment of VZV infection		
Varicella or herpes zoster	800 mg 5 times a day orally (every 4 hrs while skipping the night-time dose)	7 days
Varicella or herpes zoster in immunocompromised patients	5 mg/kg every 8 hrs intravenously	5 days (according to clinical status)
VZV infection in immunocompromised patients	10 mg/kg every 8 hrs	5 days (according to clinical status)

VZV – Varicella zoster virus, HSV – Herpes simplex virus

the dose in children below 2 years of age is half the adult dose. The dosing scheme of oral acyclovir used in the treatment of VZV infections is 20 mg/kg (max. 800 mg) 4 times a day and treatment should last 5 days. The intravenous acyclovir dosing scheme is presented in Table 4.

Dose adjustment

The doses are to be reduced in patients with impaired renal function and in the elderly. As obese patients on intravenous therapy have higher plasma acyclovir concentration, acyclovir doses should also be reduced.

In patients with impaired renal function, the doses are to be adjusted depending on the stage of kidney damage based on creatinine clearance given in mL/min in adults and adolescents, and in mL/min/1.73 m^2 in infants and children aged up to 13 years (Table 5).

In the presence of anuria, or in patients with creatinine clearance of up to 10 mL/min and in those treated with continuous ambulatory peritoneal dialysis (CAPD), the acyclovir dose is halved (2.5 mg/kg or 5 mg/kg body weight) and administered at a 24-hour interval. Hemodialysis patients receive the same dose right after the procedure and subsequently at an interval of 24 hours.

In anuric children with a GFR of 0–10 mL/min/1.73 m^2 during CAPD, it is recommended to administer half of the prescribed dose (250 mg/kg or 500 mg/m^2 body surface area or 20 mg/kg body weight) after dialysis and subsequently every 24 hours.

Tab. 4. Parenteral acyclovir dosing scheme in children (SPC Aciclovir Olikla, 2020)

Bioavailability on oral administration	10–20%	
HSV infection (except for herpetic encephalitis) and VZV infection	250 mg/m^2	Every 8 hrs
HSV encephalitis or VZV infection in immunocompromised individuals	500 mg/m^2 Body surface area	
Neonatal HSV infection	20 mg/kg body weight	

VZV – Varicella zoster virus, HSV – Herpes simplex virus

The release of the patients' health-related information was approved by the hospital authority.

Case Report 1

An 84-year-old female presented to our department with a history of left-sided headache, predominantly over her forehead and blurry vision in her left eye lasting 2 days. Her medical history was unremarkable, she was being treated only for arterial hypertension and her chronic medication listed in Table 6 included metoprolol 100 mg q.d., hydrochlorothiazide 50 mg with amiloride 5 mg q.d. and acetylsalicylic acid 100 mg q.d. On initial physical examination, there was a typical cutaneous vesicular eruption distributed across a dermatome corresponding to the left ophthalmic nerve and the patient was diagnosed with herpes zoster ophthalmicus affecting the left eye. In addition, she was seen by an ophthalmologist who described herpetic keratitis and uveitis of the left eye. Her initial laboratory findings revealed hyponatremia (117 mmol/L) and hypokalemia (3.1 mmol/L), the patient's renal parameters were within the reference ranges (urea 5.7 mmol/L and creatinine 65 μmol/L); however, the estimated glomerular filtration rate (eGFR) (Cockcroft-Gault) was 54 mL/min/1.73 m^2. The initial empiric therapy was started with parenteral acyclovir at a dose of 750 mg t.i.d., local valgancyclovir and tobramycin.

On Day 3 of hospital stay, she clinically deteriorated not responding to verbal commands and agitated. On examination, she was afebrile, her blood pressure (BP) was 118/76 mmHg, heart rate (HR) 127 bpm, respiratory rate (RR) 15–18 breaths per minute and her blood oxygen saturation level was 97%. She did not show any signs of respiratory distress, shock syndrome or cardiopulmonary insufficiency. A neurological examination described receptive and expressive aphasia and tremor, but the patient did not show any signs of meningeal irritation, lateralizing neurologic deficits or cranial nerve involvement. A brain CT scan with contrast did not provide any significant pathological findings including signs of acute hemorrhage or ischemia. However, the patient's blood tests showed hypernatremia (Na 158 mmol/L) and signs of acute renal insufficiency (urea 18.3 mmol/L, creatinine 371 μmol/L). We started with forced diuresis and reduced acyclovir dosage to 500 mg q.d. On this treatment, the patient's clinical status significantly improved and, on Day 7 (4 days after her clinical status deterioration), she was fully awake, alert, oriented to person and place, without any signs of neurological impairment. Acyclovir was stopped on Day 7, the patient returned to her baseline mental status, started physical therapy and was discharged on Day 19.

Case Report 2

A 91-year-old female with a history of ischemic heart disease, arterial hypertension, hypothyroidism, autoimmune hemolytic anemia, Parkinson's disease and diverticular disease presented to our department with an extensive herpes zoster eruption involving C4–C6 dermatomes on the left side. Her chronic medication listed in Table 6 included metoprolol 25 mg q.d., furosemide 20 mg q.d., levodopa/carbidopa 50/25 t.i.d., cyclophosphamide 50 mg q.d., pantoprazole 40 mg

Tab. 5. Acyclovir dosing in adults with renal failure (SPC Aciclovir Olikla, 2020; SPC Herpesin 400, 2020)

Infection	**Creatinine clearance**		
	50–25 mL/min	25–10 mL/min	10–0 mL/min
Herpes simplex and varicella zoster	5 mg/kg or once every 12 hrs	5 mg/kg or once every 24 hrs	
Varicella zoster and herpes simplex encephalitis	10 mg/kg body weight once every 12 hrs	10 mg/kg body weight once every 24 hrs	
Varicella and herpes zoster		800 mg every 8 hrs	800 mg every 12 hrs
Children aged 3 months to 12 years			
	25–50 mL/min/1.73 m^2	0–25 mL/min/1.73 m^2	
Herpes simplex infection caused by varicella zoster virus	250 mg/kg or 500 mg/m^2 body surface area or 20 mg/kg body weight every 12 hrs	Same dose administered every 24 hrs	Dose (250 mg/kg or 500 mg/m^2 body surface area or 20 mg/kg body weight) can be split into two doses given every 24 hrs

Tab. 6. Patients' chronic medication

Patient 1	Patient 2
Acyclovir	
Acetylsalicylic acid 100 mg q.d. Amiloride 5 mg q.d. Hydrochlorothiazide 50 mg q.d. Metoprolol 100 mg q.d.	Carbidopa 25 mg. t.i.d. Cyclophosphamide 50 mg q.d. Furosemide 20 mg q.d. Levodopa 50 mg t.i.d. Metoprolol 25 mg q.d. Pantoprazole 40 mg q.d. Quetiapine 50 mg q.d. Vitamin B12 Folic acid

q.d., quetiapine 50 mg q.d., with vitamin B12 and folic acid supplementation. Her initial blood tests were unremarkable, renal parameters were within the reference ranges (urea 4.4 mmol/L and creatinine 74 μmol/L); however, eGFR was 52 mL/min. Due to extensive vesicular herpetiform eruptions, chronic medical conditions, immunosuppressive treatment and frailty, the patient was admitted to our department, started on parenteral acyclovir 750 mg t.i.d. and stopped immunosuppressive treatment with cyclophosphamide.

On Day 5, she was found unconscious and not responding to any verbal commands. On examination, she was afebrile, her BP was 90/52 mmHg, HR 107 bpm and RR 18 breaths per minute. Neurological examination did not reveal any signs of a lateralizing neurological deficit, meningeal irritation, and her cranial nerves were intact. A brain CT scan was negative for the evidence of acute hemorrhage, ischemia, edema, or mass. However, in her laboratory findings, there were signs of acute renal insufficiency (urea 15.5 mmol/L and creatinine 542 μmol/L) and hyperkalemia (K 6.2 mmol/L). We stopped parenteral acyclovir, quetiapine, reduced metoprolol and levodopa/carbidopa dosages and started forced diuresis with crystalloids and furosemide. On this treatment, her laboratory findings improved and, on Day 10, her mental status began to clear, she became awake, alert and oriented to person. Unfortunately, the patient did not return to her physical baseline and her further clinical course was complicated by the development of pneumonia and infection caused by *Clostridiodes difficile*. Despite appropriate antibiotic and supportive treatment, the patient died on Day 36.

DISCUSSION

The above cases inspired us to review the neurologic side effects of acyclovir in detail. According to the Czech regulatory authorities, the annual consumption of oral and intravenous dosage forms of acyclovir, converted to defined daily doses (DDDs) per 1000 pop/day, was 0.5963 and 0.0114, respectively (Table 7).

The database of the Czech medical regulatory authority, the State Institute for Drug Control, included a total of 20 reports of side effects related to oral or intravenous acyclovir according to the Anatomical Therapeutic Chemical (ATC) J05AB01 code between 1 January 2013 and 31 December 2018 (Table 2). Interestingly, unlike preceding years, there was an increase in reported neurotoxic side effects

Tab. 7. Consumption of oral and intravenous dosage forms of acyclovir in the Czech Republic in 2018

	Dosage form	Number of packs	Total DDDs	DDD/1000/pop./day (mg)
J05AB01	Oral	260 617	577 294	0.5963
	Intravenous	19 521	11 085	0.0114
	Total	280 138	588 379	0.6077

Population of the Czech Republic in 2018: 10 668 641 (https://www.czso.cz/csu/czso/obyvatelstvo_lide).

Tab. 8. Reported side effects of acyclovir

Side effect reported	Incidence between 1 Jan 2013 and 31 Dec 2018 (2018)	Concomitant therapy	Age (years)
Leukopenia, pneumonia	2	Y, N	50, 37
Headache, vision disorder, vertigo	3 (1)	N	(-), >65, 42
Tingling, spasms	1 (1)	N	34
Hemiparesis	1 (1)	Y	43
Impaired consciousness	2 (2)	Y	59, 28
Skin eruptions	5 (2)	N	75, 44, 3 M, 29, <6 M
Liver test alterations	2	Y, N	(-)
Nosebleed	1	N	34
Angioedema	2 (1)	N	39, 32

(Source: State Institute for Drug Control); Y = yes, N = none, M = month

Tab. 9. Frequent side effects of acyclovir (occurring in 1/100 to 1/10 patients) (SPC Aciclovir Olikla, 2020; SPC Herpesin 400, 2020)

Side effect	Characteristics
Central nervous system disorders	Oral: headache, dizziness Intravenous: not reported
Vascular	Phlebitis
GIT	Nausea, vomiting (diarrhea and abdominal pain on oral administration)
Skin and subcutaneous tissue	Itching, rash (including photosensitivity)
General disorders and injection site reaction	Fatigue, fever

GIT – gastrointestinal tract

Tab. 10. Less frequent side effects of acyclovir (occurring in 1/1000 to 1/100 patients) (SPC Aciclovir Olikla, 2020; SPC Herpesin 400, 2020)

Side effect	Characteristics
Skin and subcutaneous tissue	Oral: urticaria, accelerated hair loss Intravenous: not available

Tab. 11. Rare side effects (1/10000 to 1/1000 patients) (SPC Acyclovir Olikla, 2020; SPC Herpesin 400, 2020)

Side effect	Characteristics
Immune system disorders	Anaphylaxis
Impaired liver and bile duct function	Oral: irreversible increase in bilirubin and liver enzymes Intravenous: transient increase in liver enzymes
Skin and subcutaneous tissue	Angioedema
Impaired kidney and urinary tract function	Increased blood urea and creatinine levels

Tab. 12. Very rare side effects (occurring in 1/10000 to 1/1000 patients) (SPC Aciclovir Olikla, 2020; SPC Herpesin 400, 2020)

Side effect	Characteristics
Blood and lymphatic system disorders	Anemia, leukopenia, thrombocytopenia
Psychiatric disorders	Agitation, confusion, hallucination, signs of psychosis
Central nervous system disorders	Tremor, ataxia, dysarthria, spasms, somnolence, encephalopathy, coma (headache and dizziness after oral administration)
Respiratory system	Dyspnea
Gastrointestinal tract	Diarrhea, abdominal pain (not reported after oral administration)
Impaired liver and bile duct function	Hepatitis, jaundice (transient rise in bilirubin levels after oral administration)
Impaired kidney and urinary tract function	Acute renal failure, pain in the kidney area

immediately associated with acyclovir therapy in 2018. A total of 5 out of 7 (71%) reported cases of neurologic symptomatology and suspected neurotoxic side effects were confirmed (Table 8).

Acyclovir therapy may be accompanied by side effects summarized in Tables 9–12.

Generally, acyclovir, if used according to the instructions for administration, belongs to drugs with a good safety profile. Therapy with acyclovir is only rarely associated with impaired renal function or even acute renal failure. It has been proposed that the underlying mechanism of kidney injury during acyclovir therapy is crystal formation in the collecting ducts resulting in obstructive nephropathy. Other possible causes of kidney injury include acute interstitial nephritis and acute tubular necrosis. Data published to date suggest that kidney injury can occur even after the first administration of the medication (Fleischer & Johnson, 2010). In exceptional cases, there may be progression to acute renal failure.

Prevention of kidney injury is relatively simple. It is crucial to avoid rapid or bolus administration and intravenous acyclovir should be administered in a 1- or 2-hour infusion. In addition, it is important to adequately hydrate the patient on high-dose acyclovir. This should prevent acyclovir precipitation in the kidney and its injury (Zhang *et al.* 2016; Andrews *et al.* 2020).

Caution is needed especially when administering intravenous acyclovir in combination with other nephrotoxic drugs, drugs eliminated by glomerular filtration or tubular secretion and in patients with impaired renal function or the elderly (Chávez-Iñiguez *et al.* 2018; Ferreira *et al.* 2018; Thind & Roach, 2017; Zhang *et al.* 2016).

Search of the Lexicomp® Drug Interactions – UpToDate platform did not reveal any known interactions between the drugs used by Patient 1. The UpToDate search box rated Patient 2's risk as D (Consider Therapy Modification) based on interactions between dopamine agonists, antiparkinson agent (levodopa) and the second-generation atypical antipsychotic drug quetiapine. Treatment with antipsychotic agents (dopamine antagonists) may worsen Parkinson's disease symptoms and reduce the efficacy of antiparkinson agents. The mechanism of this interaction is likely due to the opposing dopaminergic mechanism of action of these drugs. Antiparkinson agents increase dopamine concentration or dopamine receptor stimulation whereas antipsychotic agents have dopamine antagonist properties. (Lexicomp® Drug Interactions – UpToDate). The Lexicomp platform suggested other potential C-rated interactions (Monitor Therapy) in

Patient 2, including one between levodopa and antihypertensive medications (furosemide, metoprolol) and, possibly, between quetiapine and antihypertensive medications. Either drug combinations may result in a decrease in blood pressure or, possibly, symptomatic postural (orthostatic) hypotension (Lexicomp® Drug Interactions – UpToDate).

In high-risk patients, it might be useful to perform therapeutic drug monitoring (TDM) of acyclovir. The recommended peak concentrations are 5–15 mg/L with a mean steady-state through concentration of 0.4–1.5 mg/L (Cies *et al.* 2014/2015; Schulz *et al.* 2012).

In our case reports, the rapid increase in blood urea and creatinine levels during acyclovir therapy was presumably associated with renal impairment due to acyclovir use. Potential risk factors included advanced age and polypharmacy. The hydration status of our patients was continuously assessed, with intravenous fluid therapy provided if needed. The hypernatremia diagnosed in these cases could be iatrogenic and associated with high sodium content as one ampoule of acyclovir (250 mg of powder for solution for infusion) contains 26 mg of sodium (approx. 1.1 mmol) corresponding to approx. 1% of the WHO-recommended maximum daily intake of dietary sodium (2 g/day).

Deteriorated renal function leads to an increase in plasma acyclovir concentration and its conversion to 9-CMMG. This results in an increase in acyclovir and 9-CMMG 24-hour steady-state AUC and C_{max} in both the plasma and CSF (Helldén *et al.* 2006; Linden & Helldén 2013).

Nine-CMMG acts at the blood-brain barrier by inhibiting transporter proteins and increasing susceptibility to uremic toxicity (Smith *et al.* 2010). In addition, CMMG concentration could be monitored as a surrogate marker for neurotoxicity (Smith *et al.* 2010; von Euler *et al.* 2013). Acyclovir-induced neurotoxicity develops almost as a rule within 1–2 days of an increase in acyclovir concentration above the therapeutic range. Literature data suggest that acyclovir-related neurotoxic effects are rare, with neurotoxicity affecting mainly patients treated with intravenous acyclovir and, preferentially, patients developing renal failure (Linden & Helldén 2013; Ruiz-Roso *et al.* 2012).

Typical symptoms of overdose include neuropsychiatric symptomatology with psychotic symptoms, confusion, hallucinations, agitation, myoclonus, confusion, lethargy as well as neurological side effects such as headache, dizziness, tremor, ataxia, dysarthria, seizures, hemiparesthesia, somnolence, encephalopathy and coma. These symptoms are more common in patients treated with high doses without monitoring of fluid and electrolyte balance or those with reduced kidney function (Sadjadi *et al.* 2018; Smith *et al.* 2010;). In addition, up to 5% of patients with neuropsychiatric side effects during acyclovir therapy develop major depression with increased suicide risk (Smith *et al.* 2010).

The factors affecting neurotoxic manifestations are still poorly understood, with an increase in C_{max} and/or AUC suggested as a predictive factor (Watson *et al.* 2017).

Our case reports and published data suggest that neuropsychiatric complications are frequent and should be taken into account even before initiating parenteral therapy with acyclovir. These complications may develop after as few as 3–4 doses and progress rapidly, particularly in high-risk groups (Becerra *et al.* 2013). However, in differential diagnosis, it is important to consider also other metabolic, vascular or infectious causes. Critical information for differential diagnostic considerations is usually provided by clinical, laboratory or radiological examinations. Neuropsychiatric symptoms such as hallucination, depression, anxiety, and involuntary movements are more specific to the neurotoxic effects of acyclovir (Gentry and Peterson, 2015), while high-grade fever, headache and seizures are non-specific and more often associated with neuroinfections (Bowers & Mudrakola, 2020; Hjalmarsson *et al.* 2007).

Management of intoxication requires prompt withdrawal of acyclovir and hemodialysis and/or forced diuresis with urine alkalization. Importantly, despite its severe side effects described above, neurological complications are fully reversible after therapy withdrawal, thus it is necessary to include this side effect in the differential diagnosis of altered mental status or neurological symptoms in patients treated with acyclovir.

CONCLUSION

Acyclovir is a frequently used antiviral drug with a good safety profile. However, in high-risk groups such as the elderly, patients with impaired renal function or with multiple comorbidities on polypharmacy or those using nephrotoxic drugs, it could lead to renal impairment and an increase in plasma and CNS acyclovir concentrations with severe neuropsychiatric side effects. Thus, in high-risk patients, utmost caution should be given to the prevention of dehydration and serum ion abnormalities as well as to strict adherence to infusion therapy guidelines (prolonged infusion), monitoring of renal function, and monitoring of the patient's clinical status. Progression of side effects can be prevented in time by strict adherence to the principles of personalized medicine, individualized dosing, timely adjustment of doses and dosing schedule as well as monitoring of the patient's neuropsychological status. The neurotoxic side effects are reversible after therapy withdrawal. Thus, in patients developing mental impairment or showing other neurological symptoms during acyclovir therapy, the patient should be promptly evaluated for potential drug neurotoxicity, their therapy should be discontinued and drug elimination with forced diuresis or hemodialysis considered.

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