The importance of therapeutic drug monitoring in dosage optimization of acyclovir

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Acyclovir is an antiviral drug used to prevent and treat infections caused by herpesviruses such as herpes simplex virus and varicella-zoster virus. It is intracellularly phosphorylated into triphosphate nucleotides that inhibit viral DNA polymerase. Approximately 5–15% of acyclovir are metabolized to the main metabolite 9-(carboxymethoxymethyl)guanine (CMMG), and the main route of acyclovir elimination is renal excretion, which involves glomerular filtration and active tubular secretion. Accumulation of acyclovir and CMMG may occur in patients with impaired renal function. Acyclovir is commonly used and has good general tolerance; however, it can cause systemic adverse effects such as nephrotoxicity and neurotoxicity. Preexisting kidney disease, older age, obesity, hypertension, longer duration of treatment, and concurrent use of nephrotoxic drugs are all associated with an increased risk of acyclovir-induced nephrotoxicity. The most characteristic symptoms of neurotoxicity are confusion, somnolence, and hallucinations. Symptoms of neurotoxicity caused by acyclovir treatment may be misinterpreted as symptoms of herpetic encephalitis. It is particularly important to accurately distinguish between these two causes of neuropsychiatric symptoms, given the different treatment strategies. Determination of CMMG serum concentrations can help to differentiate between neuropsychiatric side effects of acyclovir and symptoms of any form of encephalitis. The wide interindividual variability of acyclovir pharmacokinetics can lead not only to toxicity, but also to suboptimal therapeutic concentrations of acyclovir in severe herpes virus infections. Therapeutic monitoring of acyclovir and CMMG can be a useful tool for optimizing pharmacotherapy with this antiviral drug, particularly in patients with severe clinical conditions.

Key words: acyclovir, 9-(carboxymethoxymethyl)guanine, concentrations, monitoring.

Význam terapeutického monitorování léčiv při optimalizaci dávkování acykloviru

Acyclovir je antivirotikum používané k prevenci a léčbě infekcí způsobených herpetickými viry, jako je virus herpes simplex a virus varicella-zoster. Je intracelulárně fosforylován na trifosfátové nukleotidy, které inhibují virovou DNA polymerázu. Přibližně 5–15 % acykloviru je metabolizováno na hlavní metabolit 9-(karboxymethoxymethyl)guanin (CMMG), hlavní cestou eliminace acykloviru je renální exkrece, která zahrnuje glomerulární filtraci a aktivní tubulární sekreci. U pacientů s poruchou funkce ledvin může dojít ke kumulaci acykloviru a CMMG. Acyclovir se často používá a je obecně dobře tolerován, může však způsobit systémové nežádoucí účinky, jako je nefrotoxicita a neurotoxicita. Preexistující onemocnění ledvin, vyšší věk, obezita, hypertenze, delší trvání léčby a současné užívání nefrotoxických léčiv jsou spojeny se zvýšeným rizikem nefrotoxicity vyvolané acyklovirem. Nejcharakterističtějšími příznaky neurotoxicity jsou zmatenost, somnolence a halucinace. Příznaky neurotoxicity způsobené léčbou acyklovirem mohou být chybně interpretovány jako příznaky herpetické encefalitidy. Přesné rozlišení mezi těmito dvěma příčinami neuropsychiatrických symptomů je zvláště důležité vzhledem k různým léčebným strategiím. Stanovení sérových koncentrací CMMG může pomoci odlišit neuropsychiatrické vedlejší účinky acykloviru od symptomů jakékoli formy encefalitidy. Široká interindividuální variabilita farmakokinetiky acykloviru může vést nejen k toxicitě, ale také k suboptimálním terapeutickým koncentracím acykloviru u závažných infekcí herpetickými viry. Terapeutické monitorování acykloviru a CMMG může být užitečným nástrojem pro optimalizaci farmakoterapie tímto antivirotikem, zejména u pacientů se závažnými klinickými stavy.

Klíčová slova: acyklovir, 9-(karboxymethoxymethyl)guanin, koncentrace, monitorování.

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Abbreviations:

8-OH-ACV – 8-hydroxy-9-(2-hydroxyethoxymethyl)guanine
ACV – acyclovir
ADH – alcohol dehydrogenase
ALDH – aldehyde dehydrogenase
AUC – area under the plasma concentration--time curve
C_{peak} – peak serum concentrations
C_{trough} – trough serum concentrations
CL/F – weight-adjusted apparent clearance
CMMG – 9-carboxymethoxymethylguanine
CNS – central nervous system
CSF – cerebrospinal fluid
eGFR – estimated glomerular filtration rate
HSV – herpes simplex virus
LLoQ – lower limit of quantification
NUDT15 – nucleotide diphosphatase
PCR – polymerase chain reaction
T > IC50 – time for which drug concentration remains above the 50% inhibitory concentration
VZV – varicella-zoster virus

Introduction

Human herpesviruses such as herpes simplex virus types 1 and 2 (HSV1 and 2), varicella-zoster virus (VZV), and cytomegalovirus are among the most common pathogens worldwide. They remain in the host's body for life, with clinical manifestations ranging from asymptomatic to mild and self-limiting to severe and life-threatening. Herpesviruses can cause persistent cutaneous lesions, serious organ infections (esophagitis, meningitis, severe neurological sequelae, pneumonia, and liver inflammation), and disseminated disease in immunocompromised hosts (solid organ recipients, hematopoietic stem cell transplant recipients, immunodeficiency virus infected individuals) while also being responsible for congenital infection and/or neonatal infection (1).

The antiviral era started with iododeoxyuridine which, in 1963, became the first antiviral agent used topically to treat herpes simplex keratitis. Acyclovir (ACV) was discovered in the early 1970s and was first approved for use in 1982. It is among the nucleoside analogs that reduce symptoms, virus shedding, and the frequency of outbreaks. They can be used as suppressive therapy, preemptive therapy, and risk-adapted prophylaxis. ACV is a synthetic acyclic analog of guanosine, currently available in topical, oral, and intravenous formulations, used worldwide to prevent and treat infections caused by herpesviruses such as HSV and VZV (1). ACV is intracellularly phosphorylated by viral kinases into monophosphate metabolites which are further converted into triphosphate nucleotides. It is the active form of ACV that inhibits viral DNA polymerase and is thus directly responsible for ACV's antiviral effects. Nucleotide diphosphatase NUDT15 inactivates these metabolites by converting them from triphosphate to monophosphate nucleotides, and therefore the loss of NUDT15 is linked to a higher level of active metabolites and increased drug efficacy both in vitro and in vivo. The association of NUDT15 genotype with ACV efficacy is highly relevant; therefore, NUDT15 genetic polymorphism can contribute to interindividual variability in the therapeutic effects of ACV (2).

Pharmacokinetics of ACV

After oral administration, ACV has a very low bioavailability, around 15–30% of the administered dose (3). Oral valacyclovir is a prodrug that undergoes the first-pass intestinal and/or hepatic metabolism to produce active-moiety acyclovir and L-valine at a high bioavailability that is several times greater than that obtained from oral ACV (4**)**. Protein binding of ACV is in the range of 9% to 33%. The volume of distribution of the ACV molecule is large allowing good tissue penetration, including the central nervous system (CNS) where high concentrations in the cerebrospinal fluid (CSF) are reached (3). In humans, ACV is subjected to minimal metabolism. Approximately 5–15% of ACV are metabolized in the liver by alcohol dehydrogenase (ADH) to an ACV-aldehyde which is subsequently metabolized via aldehyde dehydrogenase (ALDH) to the main metabolite 9-(carboxymethoxymethyl)guanine (CMMG). Aldehyde oxidase metabolizes ACV into 8-hydroxy-9-(-2-hydroxyethoxymethyl)guanine (8-OH-ACV). In patients without renal failure, 62.1–91.0% of intravenous ACV are excreted in urine in an unchanged form, 8.5–14.1% as CMMG, and less than 0.2% as 8-OH-ACV metabolite. The main route of ACV elimination is renal excretion, which involves glomerular filtration and active tubular secretion. In patients with renal failure, ACV elimination depends more on the metabolic pathway, which normally accounts for a small proportion of ACV elimination. The degree of this dependence increases with decreasing renal function, and a larger proportion of the ACV dose is excreted in urine as CMMG (5, 6). ACV has a half-life of 2 to 3 hours in individuals with normal kidney function and 20 hours in patients with end-stage kidney disease (7).

ACV has high interindividual variability of pharmacokinetics, which is particularly evident in younger patients, and is related to changes in renal function during the first months after birth and to body weight across the ages. In addition, the genetic status of the patient can be considered as another cause of variability in pharmacokinetics and clinical outcome. Genetic polymorphism was demonstrated not only for NUDT15 (2, 8), but also for the metabolizing enzymes ADH and ALDH (9). However, significant variability in the pharmacokinetics of ACV has been demonstrated not only between patients, but also within individual patients treated with ACV (8).

Adverse effects of ACV

ACV is commonly used and has good general tolerance. However, despite its good safety profile, it can cause systemic adverse effects such as nephrotoxicity and neurotoxicity (3).

Renal intratubular deposition of ACV crystals or direct tubular toxicity of ACV are the main mechanisms of nephrotoxicity in patients treated with intravenous ACV. By contrast, oral ACV use is not associated with an increased risk of nephrotoxicity. After the introduction of ACV into clinical practice, ACV-induced nephrotoxicity was reported in 10–48% of patients; however, in recent years, the incidence has decreased to 18–21%, which may be related to dose adjustment, slow infusion of ACV, and adequate intravenous hydration of the patient. Preexisting kidney disease, older age, obesity, hypertension, longer duration of treatment, and concurrent use of nephrotoxic drugs are all associated with an increased risk of ACV-induced nephrotoxicity. Monitoring of renal function and dose adjustment of ACV are

necessary in patients with renal impairment to avoid the risk of accumulation leading to toxic drug and metabolite concentrations (6, 10). On the other hand, it is important to realize that the wide intra- and interindividual variability of ACV pharmacokinetics can lead not only to toxicity, but also to suboptimal therapeutic concentrations of ACV in severe HSV and VZV infections. Dosing adaptations are currently only prescribed for renal impairment, and there are few recommendations for patients with enhanced renal function. Augmented renal clearance, with an incidence of 16–80%, is a common occurrence in critically ill patients, and is characterized by increased creatinine clearance and elimination of renally eliminated drugs. For these patients, there is often no recommendation to adjust the dosage of this type of drug (5).

The neurotoxicity induced by ACV is a poorly known and rare adverse effect that can occur particularly in patients with advanced age (> 65 years old), impaired renal function (acute or chronic renal failure), and high doses of ACV. Clearance of ACV is primarily renal and crosses the blood-brain barrier; therefore, a decrease in glomerular filtration rate can increase CSF concentrations and cause neurotoxicity. However, there have been case reports describing CNS symptoms in individuals without renal failure. Additional predisposing factors include simultaneous treatments with other neurotoxic drugs and severe illness. Symptoms of neurotoxicity have also been reported in ACV-treated patients with various malignancies and in bone marrow transplant recipients. They were observed after intravenous as well as oral treatment with ACV. Despite the fact that the neurotoxicity mechanism of ACV is not completely understood, a proposed hypothesis would be cellular alteration through the inhibition of DNA polymerase at the mitochondrial level. Neuropsychiatric signs and symptoms, such as confusion, altered level of consciousness, hallucinations, dizziness, drowsiness, stupor, coma, agitation, dysarthria, tremor, and myoclonus are exceedingly prevalent (3, 11–13).

Helldén and colleagues reported several cases of the so-called Cotard syndrome as an adverse drug reaction to ACV and its prodrug valacyclovir. Jules Cotard first described his eponymous syndrome, a rare psychiatric condition with strong ideas of death, in the 1880s (14). Patients of the Swedish authors reported that their body felt unfamiliar, they felt shut off from the surrounding world, they had anxiety, fear, slurred speech, and visual and auditory hallucinations, and they believed they were dead. They had also difficulty walking, cried out, and appeared terrified. The feeling of being dead occurred repeatedly and the patients were convinced that everyone around them was dangerous. After Cotard's syndrome subsided, it was followed by hemineglect syndrome, similar to alien hand syndrome. Cotard's syndrome has been associated with severe somatic stress as well as general and localized cerebral pathologies. Findings reported by Helldén et al. add the adverse reaction to an antiviral drug as another cause and provide clues to the syndrome's possible neuropsychiatric origin. Clinicians should be aware of the association between body scheme disturbances and (val)acyclovir (11–14). VZV is one of the most common viral agents causing CNS infection which can manifest as aseptic meningitis, encephalitis, myelitis, and vasculopathy. ACV is used to treat these infections; however, it can have neurotoxic effects that can mimic the manifestations of varicella zoster CNS disease. Therefore, in patients with VZV infection treated with ACV and neurological symptoms, it is very difficult to make a correct differential diagnosis of neurotoxicity with respect to viral encephalitis. It is particularly important to accurately distinguish between VZV encephalitis and ACV-induced neurotoxicity, given the different management strategies (15). Clinically, CNS symptoms caused by ACV treatment may be misinterpreted as symptoms of herpetic encephalitis, contributing to the physician's decision to increase the dose of ACV rather than decrease it. Patients with Cotard's syndrome and renal failure should preferably be referred to a dialysis unit, not to the department of psychiatry (11–14).

Neuropsychiatric side effects, especially confusion, somnolence, and hallucinations, were observed as the most common neurological manifestations of ACV neurotoxicity, particularly in patients with impaired renal function. By contrast, viral encephalitis is characterized by the presence of fever, headache, meningeal symptoms such as neck stiffness, and cranial neuropathy. The presence of pleocytosis and a positive polymerase chain reaction (PCR) or antibodies to VZV in the CSF are also indicators of viral infection. On the other hand, false-positive results with the molecular PCR panel have been documented as well (15). Neurotoxicity occurs after 3 days of treatment and reverses completely within 1–5 days following ACV discontinuation, depending on whether the patient undergoes dialysis, whereas encephalitis occurs 7 days after the appearance of skin lesions (3, 15). Neurotoxicity has been described to a lower extent compared to nephrotoxicity. Combined simultaneous ACV-induced nephrotoxicity and neurotoxicity have also been described rarely (4).

The basis of treatment of ACV toxicity is its discontinuation and, in some cases, further elimination by dialysis may be required (3). Hemodialysis, hemofiltration, and hemodiafiltration are all extracorporeal procedures that are effective at removing ACV because of its small molecular weight (225 Da), low plasma protein binding, low steady-state volume of distribution, and high water solubility (4).

Pharmacodynamics and therapeutic monitoring of ACV concentrations

ACV displays time-dependent killing. Its efficacy in the treatment of HSV and VZV infections has been linked to the area under the plasma concentration-time curve (AUC) and the duration for which the drug concentration remained above the 50% inhibitory concentration ($T > IC50$). The T > IC50 target that has been proposed is 50% of the dosing interval. However, controversy exists regarding which of these pharmacodynamic parameters is most important in predicting clinical success. Despite the fact that ACV has been available on the market for many years and successful treatment of patients using ACV plasma concentrations as a treatment guide was reported as early as the 1990s, there are still limited data linking ACV exposure to clinical efficacy and toxicity (5, 6).

It has been shown that serum CMMG concentration is consistently increased in patients with ACV-induced neurotoxicity, particularly

in those with acute or chronic kidney disease. In Sweden, measurements of CMMG levels have been used as a marker of ACV-induced toxicity since 1994 and helped many Swedish physicians to distinguish between ACV neurotoxicity and symptoms of viral encephalitis infections (6, 11–13). ACV plasma peak concentrations above 25 mg/L are the limit considered to result in moderate or severe adverse effects such as nausea, abdominal pain, vomiting, renal failure, and neutropenia. A peak higher than 50 mg/L has been proposed as a factor for an increase in the risk of neurotoxicity (16). In contrast to serum CMMG concentrations where values higher than 2.4 mg/L have been shown to pose a risk of neurotoxicity, no consensus has yet been reached on the reference range for trough and peak ACV serum concentrations. However, it is important to note that the interpretation of CMMG concentrations depends on the indication for treatment. While higher concentrations of CMMG may be acceptable for the treatment of herpes encephalitis, lower concentrations may be unacceptable for the prophylaxis of postherpetic neuralgia. Therefore, the usefulness of ACV treatment in individual patients should be evaluated considering the efficacy and severity of treatment against the risk of side effects.

Individual monitoring of ACV and CMMG serum concentrations combined with the use of Bayesian population modeling is a useful tool for ACV dose adjustment, aiding in optimizing therapy, particularly in patients with severe clinical conditions (5, 11–13, 16). Unfortunately, the values related to the possible reference range are reported inconsistently in the literature, especially for ACV, by various authors (Table 1) (8, 12, 16–23).

Our prospective study results (5)

At our department (the Department of Clinical Pharmacology, Institute of Laboratory Medicine, University Hospital Ostrava, Czech Republic), we conducted a prospective study in which data were analyzed in 27 patients who were treated with ACV between June 2019 and October 2021 at the Clinic of Infectious Medicine, University Hospital Ostrava, Czech Republic. ACV was administered intravenously; the infusion duration was 1 hour. The patients were mostly hospitalized in a standard ward, and the initial dosage of ACV and any dose adjustment were determined based on the renal function of the patients and at the discretion of the attending physician. According to the clinical condition of the patient and the decision of the attending physician, intravenous hydration was provided. Total serum concentrations of ACV and CMMG were analyzed using ultra-high-performance liquid chromatography–tandem mass spectrometry at our department (24).

Blood samples were collected between days 4 and 10 (median, 5 days) after starting treatment before the morning dose (so-called "trough" concentration) and 1–40 min (median, 30 min) after the end of the infusion (so-called "peak" concentration). For statistical calculations, half of the lower limit of quantification (LLoQ) concentration was used for samples with concentrations lower than LLoQ. Weight-adjusted apparent clearance (CL/F) was calculated for ACV as follows: CL/F (L/kg) = daily dose (mg/kg) / trough serum concentration of ACV (mg/L). The patients were divided into two subgroups according to the values of estimated glomerular filtration rate (eGFR; below and above 1 mL/s/1.73 m^2) reported by the local biochemical laboratory (reference range = 1.00–2.35 mL/s/1.73 m^2) and obtained from the hospital information system at the time of collection of ACV concentrations. The age, weight, and height of the patients, ACV dosing, CL/F, and ACV and CMMG concentrations and their ratios were compared between patients with normal and reduced renal function. The paired values of the eGFR, serum creatinine concentration, and serum urea concentration obtained at the time of collection of ACV concentrations were compared with the data obtained before the start of ACV treatment. The relationship between ACV and CMMG concentrations and ACV dose, serum creatinine concentration, serum urea concentration, and eGFR was evaluated. We also analyzed the relationship between trough and peak concentrations of ACV and CMMG.

The patients in the subgroup with reduced renal function were notably older, smaller, and of lower body weight, and received a significantly lower dose of ACV. However, even with lower-dose ACV administration, the trough ACV concentrations and both CMMG concentrations were significantly higher in the subgroup with reduced renal function. The CMMG/ACV serum concentration ratio was also higher in the subgroup with reduced renal function both before (trough concen-

Tab. 1. *Review of literature*

Reference	Diagnosis	ACV-C_{trough} (mg/L)	ACV-C_{peak} (mg/L)	CMMG (mg/L)
Abdul-Aziz MH, et al. (17)	critically ill patients	2.0–4.0		
Cies JJ, et al. (18)	life-threatening HSV infections in neonates	≥ 3.0		
Euler M, et al. (19)	herpes encephalitis	< 2.3	20.7	C_{trough} 0.48–1.44
Lycke J, et al. (20)	multiple sclerosis		0.4–2.0	
Yang HH, et al. (21)	herpes zoster infection	0.12–10.8		
Helldén A, et al. (12)	adult herpes virus infections			< 2.4
Abdalla, et al. (16)	prevention and treatment of HSV and VZV infections in children	> 0.56 (HSV) > 1.125 (VZV)	25.0	
Schulz M, et al. (22)	herpes zoster infection	0.4–1.5	5.0–15.0	
Feldman S, et al. (23)	herpes zoster infection	< 2.5–4.5		
Maximova N, et al. (8)	prevention and treatment of HSV and VZV infections in children	> 0.5	< 25.0	

ACV – acyclovir; CMMG – 9-carboxymethoxymethylguanine; C_{trough} – trough serum concentration; C_{peak} – peak serum concentration; HSV – herpes simplex virus; VZV – varicella-zoster virus (8, 12, 16–23)

tration) and after (peak concentration) ACV administration. The study found no correlation between serum ACV and CMMG concentrations and the daily dose of ACV and dose per kilogram of body weight. Regarding other renal functions, both trough and peak ACV concentrations showed a significant inverse correlation only with eGFR obtained at the time of collection of ACV concentrations. By contrast, a significant correlation was found between the trough concentrations of CMMG and serum creatinine concentrations, serum urea concentrations, and eGFR obtained the time of collection of ACV concentrations. A significant correlation was also demonstrated between the peak concentrations of CMMG and serum urea concentrations as well as eGFR obtained at the time of collection of ACV concentrations. As a sign of nephrotoxicity, we observed an increase in serum creatinine concentrations of ≥ 40 µmol/L or 30% compared to baseline in one patient only (4% of the study group). Paired values of eGFR, serum creatinine concentration, and serum urea concentration obtained at the time of collection of ACV concentrations were not statistically different from those obtained before the initiation of ACV treatment. The study further demonstrated a 10-fold difference in the weight-adjusted apparent clearance of ACV between individual patients (3.1 to 30.4 L/kg)

We concluded that wide interindividual variability in ACV pharmacokinetics may lead to toxicity as well as to suboptimal therapeutic concentrations of ACV in severe HSV and VZV infections. We have also confirmed that serum concentrations of the potentially neurotoxic metabolite CMMG are significantly correlated with markers of renal function, particularly with eGFR values measured during ACV treatment. In addition, data of patients receiving oral ACV were later analyzed. Basic characteristics of the study groups (intravenously and orally administered ACV) and details of treatment are shown in Table 2; markers of renal function obtained before the first dose of ACV and at the time of collection of ACV concentration, trough and peak serum concentrations of ACV and CMMG, and weight-adjusted apparent clearance of ACV are given in Table 3. A few examples from routine therapeutic monitoring of ACV performed at our department are shown in Figures 1–4. The MWPharm 3.30 software was used for pharmacokinetic analysis; the reference range of ACV C_{trough} = 0.1–10.8 mg/L, C_{peak} ≤ 20.3 mg/L, CMMG both before and after administration < 2.4 mg/L.

Conclusions

ACV is an effective drug used to prevent and treat infections caused by HSV and VZV, but it exhibits high intra- and interindividual variability regarding pharmacokinetic parameters and treatment response. It has a high potential for nephrotoxicity and neurotoxicity in patients with reduced kidney function; therefore, dose adjustment based on kidney function is mandatory, particularly in oliguric and dialysis-dependent patients. Symptoms of neurotoxicity caused by ACV treatment may be misinterpreted as symptoms of herpetic encephalitis. It is of particular importance to accurately distinguish between these two causes of neuropsychiatric symp-

Tab. 2. *Basic characteristics of study groups (intravenously and orally administered acyclovir) and details of treatment*

	Day of sampling	Age (years)	Weight (kg)	Height (cm)	Dose (mg/day)	Dose (mg/kg/day)
intravenous administration (number = 27)						
median range	5 4–10	76 14–93	74 55–118	170 150–195	2 250 650–2 700	29.2 9.6–32.1
mean ± SD	5 ± 2	70 ± 20	78 ± 16	169 ± 11	1 980 ± 529	25.6 ± 6.5
oral administration (number = 7)						
median range	5 4–7	81 29–84	72 50–102	165 150–172	4 000 2 000–4 000	50.6 23.5–80.0
mean±SD	5 ± 1	67 ± 21	75 ± 17	163 ± 8	3 486± 886	49.9 ± 20.0

Tab. 3. *Serum creatinine concentrations and estimated glomerular filtration rate (eGFR) obtained before the first dose of acyclovir (time "1") and at the time of sampling acyclovir concentration (time "2"); trough (Ctrough) and peak (Cpeak) serum concentrations of acyclovir (ACV) and 9-carboxymethoxymethylguanine (CMMG) and their ratio; weight-adjusted apparent clearance (CL/F) of ACV*

	creatinine 1 (µmoL/L)	creatinine 2 (µmoL/L)	eGFR 1 (mL/s/ 1.73 m²)	eGRF 2 (mL/s/ 1.73 m²)	ACV C_{trough} (mg/L)	ACV C_{peak} (mg/L)	CMMG C_{trough} (mg/L)	CMMG C_{peak} (mg/L)	CMMG/ ACV ratio C_{trough}	CMMG/ ACV ratio C_{peak}	CL/F (L/kg)
intravenous administration											
number	27	27	27	27	26	25	26	25	26	25	26
median range	88 43–153	83 43–152	1.09 0.42–2.31	1.17 0.43–2.27	2.4 0.8–7.6	14.0 6.3–25.7	0.85 0.12–2.30	1.30 0.47–2.70	0.32 0.07–0.63	0.11 0.03–0.24	10.4 3.1–30.4
mean±SD	91 ± 27	87 ± 25	1.14 ± 0.45	1.19 ± 0.45	3.0 ± 1.9	14.2 ± 5.0	0.89 ± 0.61	1.45 ± 0.71	0.31 ± 0.16	0.11 ± 0.05	11.4 ± 6.5
oral administration											
number	7	7	7	7	6	6	6	6	6	6	6
median range	69 48–221	65 49–185	1.19 0.38–2.13	1.36 0.47–2.12	1.7 0.4–3.8	2.1 0.6–2.8	0.47 0.03–1.40	0.35 0.06–0.79	0.30 0.08–0.42	0.16 0.10–0.28	38.6 13.1–69.4
mean±SD	93 ± 59	83 ± 47	1.20 ± 0.56	1.29 ± 0.52	1.8 ± 1.2	2.0 ± 0.8	0.57 ± 0.47	0.38 ± 0.24	0.28 ± 0.14	0.17 ± 0.06	37.7 ± 22.4

Fig. 1. *Case report No. 1*

In a patient with dg. herpes zoster thoracis l. sin. with impetiginization (concomitant diagnosis of ulcerative colitis, biological treatment) during oral therapy with acyclovir, there was a general alteration of the clinical condition (fever, joint and muscle pain, weakness, fatigue), therefore he was admitted for intravenous ACV therapy. For the first two days, a dose of 750 mg every 8h was applied, then the dose was increased to 850 mg every 8 h. At this dose, a trough concentration of ACV = 1.7 mg/L (CMMG = 0.27 mg/L) was measured and in 25 min after the infusion, the concentration of ACV = 8.9 mg/L (CMMG = 0.64 mg/L) was determined. The patient responded well to the treatment, the herpetic morphs gradually dried up into crusts, the impetiginization healed, there were no neuralgias, and he was discharged in an overall good clinical condition

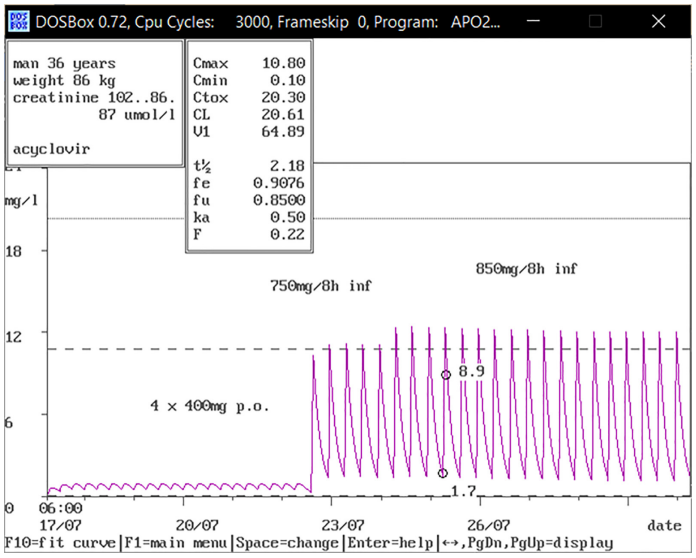


Fig. 2. *Case report No. 2*

Patient with dg. herpes zoster ophthalmicus l. sin. with conjunctivitis and incipient keratitis was admitted for intravenous acyclovir therapy. There was a worsening of renal function, the patient was slightly confused, especially at night, the dose was therefore reduced from the initial 750 mg every 8 h to 750 mg every 24 h. Then the trough concentration of ACV = 3.2 mg/L and CMMG = 1.0 mg/L was measured (ratio 0.31), peak concentration of ACV was 25.7 mg/L and CMMG 1.2 mg/L. Unfortunately, concentrations were not determined before dose reduction, from pharmacokinetic analysis it can be estimated that the trough concentration of ACV was around 19.0 mg/L and CMMG (at a ratio of at least 0.31) around 6.0 mg/L, which can be evaluated as very suspected contribution to neuro- and nephrotoxicity

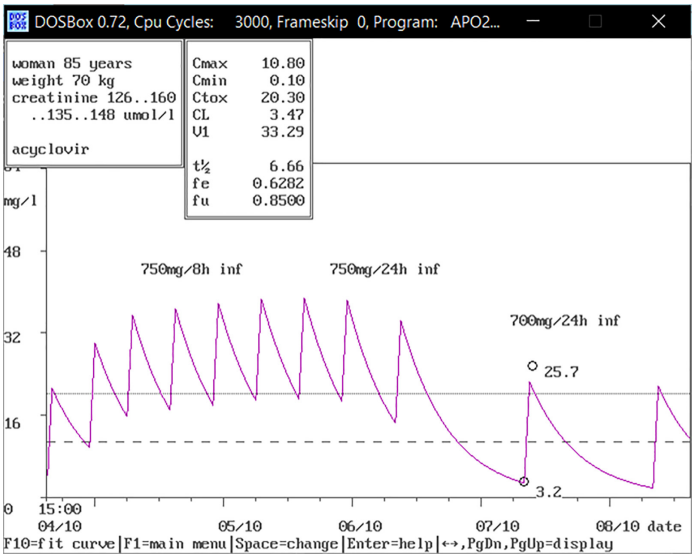


Fig. 3. *Case report No. 3*

Patient with dg. herpes zoster thoracis l. sin. was admitted to the ICU of the Neurological clinic for psychomotor restlessness, lightly sedated but contactable, capable of adequate responses, brain CT without pathology, intravenous acyclovir was administered. In two days, he was transferred to the ICU of the Infectious disease clinic for suspected neuroinfection, which was not confirmed by lumbar puncture, there was a progressive impairment of consciousness, respiratory insufficiency requiring intubation, and progression of acute non-oliguric renal failure. Over the next two days, the patient was transferred to the anesthesiology-resuscitation department, extensive ischemia was demonstrated on a CT scan of the brain, the patient had hemodynamic failure and non-oliguric renal failure without the need for elimination, sedation was gradually reduced, but without signs of consciousness, a transcranial sono with finding of chronic occlusion of ACI l. dx. The neurological examination stated: "cerebral ischemia is no longer treatable, but it alone does not explain the patient's condition (coma with the need for UPV and circulatory instability), rather it is secondary to this, the primary involvement is not clear." Based on the determined concentrations of ACV and CMMG, it is possible to suspect ACV-induced nephro- and neurotoxicity (trough ACV concentration = 19.7 mg/L and CMMG = 15.6 mg/L; peak ACV concentration = 40.7 mg/L and CMMG = 15.3 mg/L)

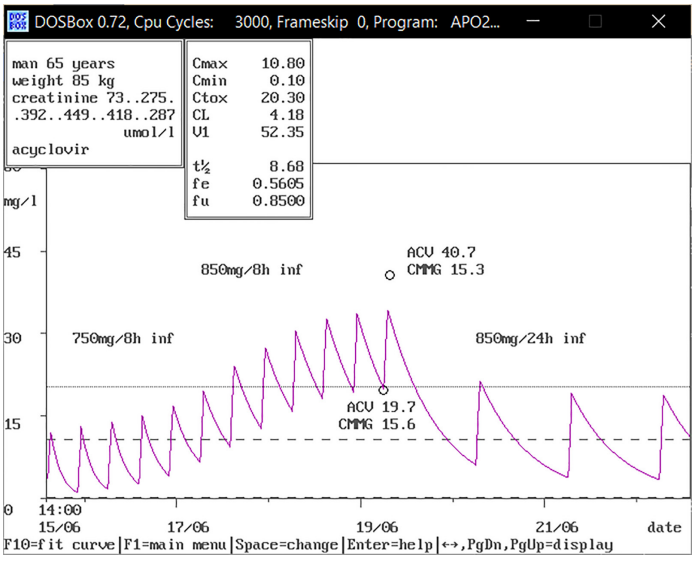
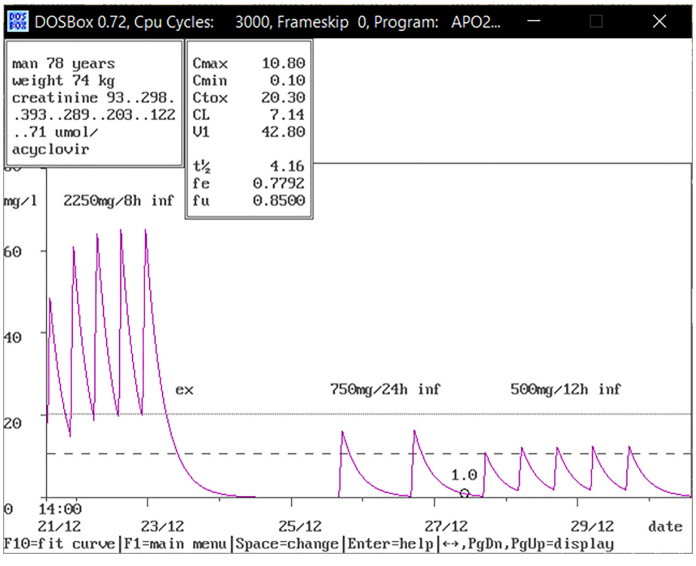


Fig. 4. *Case report No. 4*

Patient with dg. herpes zoster thoracicus l. sin. with generalization and impetiginization was admitted for intravenous administration of acyclovir, but by mistake several times instead of 750 mg every 8 h he received 3 × 750 mg every 8 h (i. e. a 3-fold dose). On the 3rd day, he began to feel worse, reported neurological problems (change in color of objects, movement of walls), therefore acyclovir was temporarily discontinued and the patient was transferred to the ICU. He gradually became totally disoriented to place, time and person, was restless, had hallucinations and slurred speech. Later he was somnolent to soporific, without verbal contact. Subsequently, he became awake to being addressed, but his speech was still slurred and unintelligible. At the same time, renal function deteriorated. These problems lasted for about 3 days, after which the condition improved relatively quickly, including the normalization of renal functions. Acyclovir was restarted at a reduced dose of 750 mg every 24 h, when the trough concentration of ACV was 1.0 mg/L and CMMG 0.42 mg/L (ratio 0.42). The concentration of acyclovir at the time of the patient's problem was not determined, but it can be estimated from the pharmacokinetic analysis that the trough concentration of ACV was around 20.0 mg/L at that time and the CMMG concentration was (at a ratio of at least 0.42) at least 8.4 mg/L. The patient was discharged with a diagnosis of encephalopathy and acute renal failure as an adverse effect of acyclovir



toms, given the different treatment strategies. Determination of CMMG serum concentrations can aid in differentiating between neuropsychiatric side effects of ACV and symptoms of any form of encephalitis. In the case of ACV-induced neurotoxicity, hemodialysis effectively relieves CNS side effects and decreases serum concentrations of ACV and CMMG.

The wide interindividual variability of ACV pharmacokinetics can lead not only to toxicity, but also to suboptimal therapeutic concentrations of ACV in severe HSV and VZV infections. Therapeutic monitoring of ACV and CMMG, combining measurement of serum drug concentrations with Bayesian estimation from a population model, can be a useful tool for optimizing pharmacotherapy with this antiviral drug, particularly in patients with severe clinical conditions.

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