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Acute renal and neurotoxicity due to weight-based dosing of intravenous acyclovir: How to dose in obese patients?

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ABSTRACT

Background: Acyclovir is a hydrophilic drug that is mainly distributed in the lean compartments of the body. Consequently, dosing on total body weight in obese patients may lead to drug overdosing. Inconsistency in clinical guideline recommendations and a lack of clear recommendations in the Summary of Product Characteristics on how to dose acyclovir in obese patients can impede safe and effective treatment.
Case report: This report describes a 71-year-old obese patient (body mass index 35 kg/m^2) with herpes zoster ophthalmicus and meningoencephalitis. The patient had normal renal function and was treated with acyclovir with a dosage based on actual body weight (10 mg/kg q8h intravenously). Supratherapeutic acyclovir concentrations probably induced acute kidney injury (AKI) and neurotoxicity.
Results: Due to the severity of the toxic effects, multiple sessions of hemodialysis were necessary, with eventual full recovery of the renal function and neurotoxic symptoms. Low dose haloperidol and lorazepam were not effective in resolving audiovisual hallucinations in our patient.
Conclusion: This case report emphasizes the need for adjusted dosing and subsequent close monitoring of obese patients who are treated with hydrophilic drugs, such as acyclovir, to avoid patient harm. We discuss prevention and management strategies for acyclovir toxicity in obese patients based on the current literature.

Background

Acyclovir is a hydrophilic drug used for the treatment of herpes simplex virus (HSV 1 and 2) and varicella-zoster virus (VZV) infections. In case of serious infections with involvement of the central nervous system, such as encephalitis or meningitis, high-dose acyclovir is administered, namely a weight-based intravenous (IV) dose of 10 mg/kg q8h if renal function is normal (estimated glomerular filtration rate (eGFR) > 50 ml/min/1.73 m^2).

Supratherapeutic plasma concentrations of acyclovir can result in insoluble crystal formation in the kidneys, which subsequently can lead to acute kidney injury (AKI). Risk factors for supratherapeutic acyclovir levels, such as rapid infusion time, hypovolemia and excess dosage in patients with (chronic) kidney disease are therefore associated with a higher risk of acyclovir-induced AKI [1]. Neurotoxicity can be another sign of acyclovir overdosing, which can parallel the decrease in the renal function but can also occur if normal eGFR is preserved [2,3].

Acyclovir is a hydrophilic drug with a volume of distribution (Vd) of 0.6 L/kg and a partition coefficient (log P) of −1.56 [4]. Therefore, acyclovir is distributed in the 'lean' body compartment, which consists of all the 'non-fat' mass-like muscles and the vascular system. The body composition of a 'normal weight' individual (body mass index (BMI) 18.5–25 kg/m^2) is approximately 20% fat and 80% lean mass, but in obese individuals (BMI ≥ 30 kg/m^2) it is roughly shifted to 40% fat mass and 60% lean mass [5]. Dosing acyclovir on actual body weight (ABW) in obese patients may thus lead to supratherapeutic plasma concentrations because acyclovir distributes proportionally less in the excess fat tissue.

The pharmacokinetics of acyclovir in obese patients has not been well studied. This leaves clinicians with a dilemma: dosing obese patients on ABW poses a high risk for toxic acyclovir concentrations, whereas dose reduction based on adjusted body weight (AdjBW), ideal body weight (IBW) or lean body weight (LBW) may lead to undertreatment in patients suffering from a severe viral infection. The SmPC of acyclovir warns – based on a single-

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dose pharmacokinetic study – for high plasma levels in obese patients when acyclovir is dosed on ABW. Yet, no recommendations about dose adjustments for this patient population are provided in the SmPC [6]. Internationally, some clinical guidelines suggest not to dose on ABW in obese patients. However, dose recommendations remain inconsistent, recommending dose adjustments based on either AdjBW, IBW or LBW [7–10]. For instance, the University of Michigan Health System recommends a dose adjustment based on adjusted body weight (AdjBW) in patients with a BMI > 30 kg/m^2, whereas others suggest dosing on ideal body weight (IBW) for patients with a BMI > 30 kg/m^2 [8,10]. Other acknowledged sources, such as IBM Micromedex, do not specifically mention dose adjustments for obese patients [9]. In clinical practice, this lack of uniformity in dose recommendations can lead to inconsistency in dosing practices of IV acyclovir and potentially leads to patient harm [7,11].

This report describes an obese patient with herpes zoster ophthalmicus and meningoencephalitis who developed severe acyclovir-induced acute kidney injury followed by neurotoxicity after unadjusted dosing of intravenous acyclovir.

Case report

A 71-year-old woman (165 cm, 95 kg, BMI 35 kg/m^2) was admitted to the medium care (MC) facility of the University Medical Center Utrecht (UMCU), the Netherlands, with a fever due to progressive herpes zoster ophthalmicus and a suspicion for varicella zoster virus (VZV) meningoencephalitis. Two days prior to admission, the general practitioner had initiated valacyclovir (500 mg q8h orally) and acyclovir 3% ophthalmic cream.

Fever (40.1 °C) and tachycardia (heart rate 127/min) were present at admission. Blood pressure was 117/65 mmHg. Renal function was within normal range with a serum creatinine level of 62 μmol/L, corresponding to an eGFR (CKD-EPI) of 87 ml/min/1.73 m^2, and a blood urea nitrogen (BUN) level of 4.6 mmol/L (ref. 3.0–7.5 mmol/L). The potassium level was 4.0 mmol/L (ref. 3.8–5.0 mmol/L). The sodium level was low – 128 mmol/L (ref. 136–146 mmol/L) – for which 1L 0.9% sodium chloride infusion was initiated directly on admission, followed by a 1.5L 0.9% sodium chloride infusion per 24 hours for the consecutive days. Laboratory values over time are listed in Table 1.

The patient also suffered from COPD GOLD 2 and Addison's disease, which were well controlled with chronic corticosteroid suppletion (hydrocortisone, fludrocortisone and dehydroepiandrosterone). Other drugs on admission were inhaled tiotropium/olodaterol, low dose acetylsalicylic acid, calciumcarbonate, colecalciferol, oxycodone, timolol/latanoprost and hypromellose eye drops.

Due to insufficient effect or oral valacyclovir, antiviral treatment was changed on the first day of admission to parenteral acyclovir. PCR results confirmed the initial suspicion for a VZV meningoencephalitis, which required intravenous high-dose acyclovir treatment based on local protocol. According to the SmPC and the national antibiotic guideline recommendations [6,12] the acyclovir dosage of 10 mg/kg (950 mg) q8h based on ABW was prescribed and administered as slow intravenous infusion (over 60 minutes). After the administration of the first two acyclovir doses, decrease in urinary production was noted, without urinary retention on bladder scan. The creatinine level measured after six administrations had raised from 62 μmol/L at baseline to 336 μmol/L (day 3), corresponding to an eGFR of <20 ml/min/1.73 m^2 (Fig. 1). The acyclovir plasma concentration was 41.3 mg/L three hours after the sixth administration (reference peak concentration 20.7 ± 10.2 mg/L (C_{max}); reference trough concentration 2.3 ± 1.4 mg/L ($C_{min,8h}$)) [4]. By this time, the patient also suffered from audiovisual hallucinations. The acyclovir treatment was immediately stopped after considering the AKI and neurotoxicity as a result of acyclovir administration. Evaluation of the chronic medication concluded to have no influence on the development of neurotoxicity and AKI and was therefore not altered or discontinued. The patient had no history of psychiatric illnesses prior to acyclovir treatment. Treatment of audiovisual hallucinations with haloperidol 1 mg po bid and lorazepam 0.5 mg po qd did not result in improvement of the mental status. As the patient suffered from both severe neurological effects and anuria, hemodialysis was started on the fourth day after the first administration of intravenous acyclovir.

After four hours of standard intermittend hemodialysis (ultrafiltration (UF) volume 260 ml; UF rate 250 ml/min; dialysate bicarbonate concentration), the acyclovir plasma concentration decreased to 8.6 mg/L, and the creatinine level decreased from 400 μmol/L to 163 μmol/L (day 4, see Fig. 1). The next morning, a second four-hour standard intermittend hemodialysis session (UF volume 300 ml; UF rate 250 ml/min; dialysate bicarbonate concentration) was initiated, which further reduced the acyclovir plasma level to 0.7 mg/L. Hallucinations gradually disappeared after the two dialysis sessions. Renal function fully recovered, with a creatinine level of 79 μmol/L on day 8 and 56 μmol/L on day 11 (eGFR > 90 ml/min/1.73 m^2). Sixty hours after the second dialysis session, oral famciclovir was initiated in a standard dosage (500 mg q8h) because of its lower risk of nephrotoxicity [2,13]. On day 13, the patient was discharged with oral famciclovir. After a total treatment duration of three weeks, all VZV lesions had disappeared. Famciclovir was continued for one year in a prophylactic dosage of 500 mg once daily.

Table 1
Laboratory values over time since admission to the hospital (=day 1) until day 5 of admission.

	Admission (Day 1)	Day 3	Day 4	Day 5	Reference
Serum					
Sodium	128	126	131	137	(136–146 mmol/L)
Potassium	4.0	4.0	4.8	3.8	(3.8–5.0 mmol/L)
Ureum	4.6	16.0	18.6	–	(3.0–7.5 mmol/L)
Creatinine	62	336	413	204	(49–90 umol/L)
eGFR (CKD-EPI)	87	<20	<20	21	(>90 ml/min/1.73 m^2)
Alkaline phosphatase	76	–	–	–	(0–120 U/L)
Gamma-GT	60	–	–	–	(0–40 U/L)
ASAT	55	31	–	–	(0–30 U/L)
ALAT	54	31	–	–	(0–35 U/L)
LD	288	272	–	–	(0–250 U/L)
CRP	161	56	–	–	(0–10 mg/L)
Thrombocytes	141	155	–	–	(150–450 × 10^9/L)
Leukocytes	5.5	10.6	–	–	(4–10 × 10^9/L)

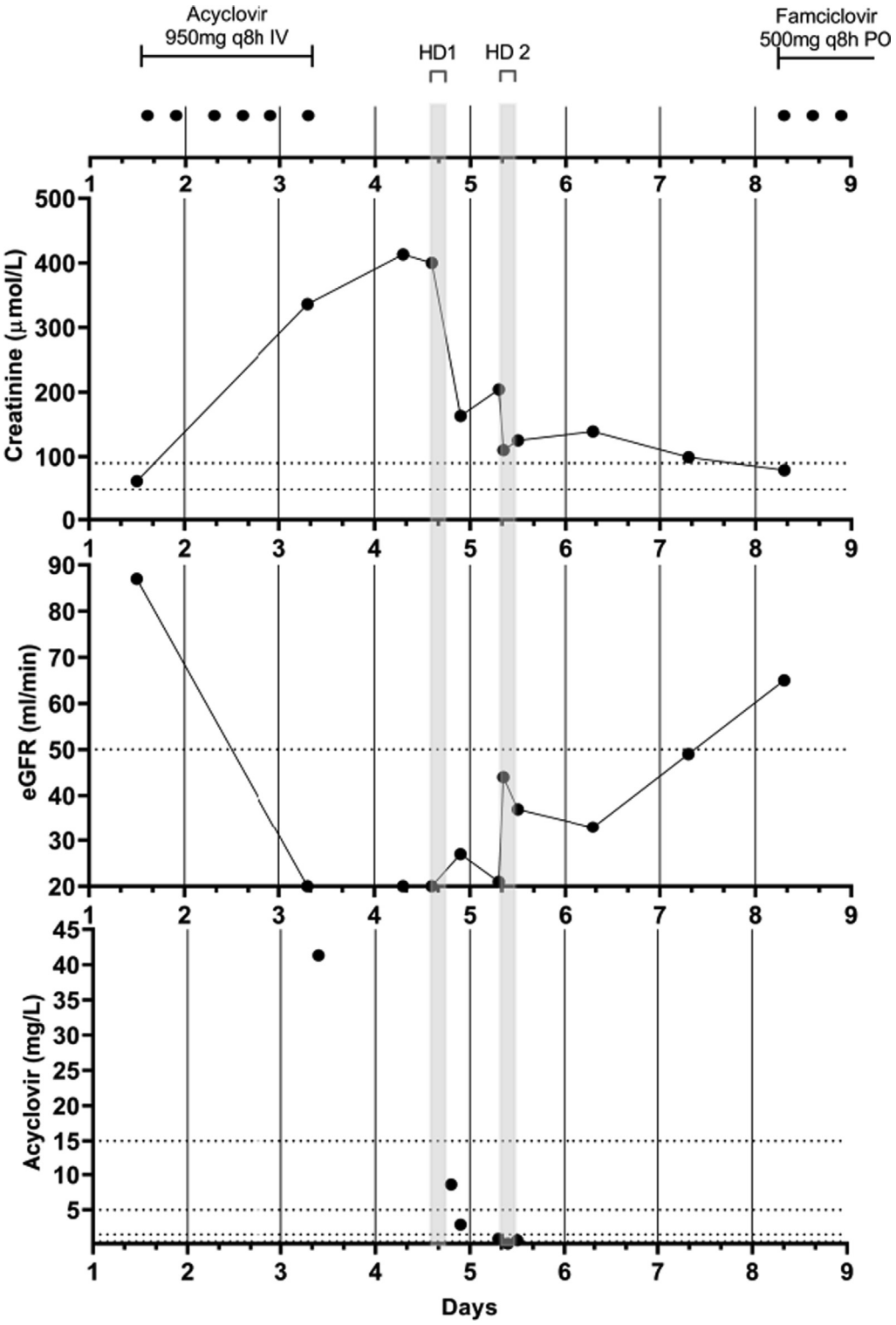

Fig. 1. Creatinine, estimated Glomerular Filtration Rate and acyclovir plasma concentration over time since admission to the hospital (=day 1) until day 8 of admission. IV = Intravenous; PO = per os; HD1 = first hemodialysis session (4 hours). HD2 = second hemodialysis session (4 hours).

Discussion

We present a case of an obese patient who developed AKI and neurotoxicity after treatment with high-dose (10 mg/kg IV q8h) acyclovir based on ABW. As the acyclovir dosage was not adjusted for the altered body composition in our patient, this most likely resulted in toxic acyclovir plasma concentrations, with severe renal- and neurotoxicity as a result. Hemodialysis and prolonged hospitalization were necessary.

Literature review

Three similar cases of severe acyclovir-induced toxicity in obese patients have been published. All patients weighted over 100 kg and were treated for confirmed or suspected viral encephalitis or

meningitis. All three patients developed AKI, and two patients developed neurotoxicity as a result of 10 mg/kg q8h IV acyclovir based on ABW [14–16]. All patients had an adequate renal function at treatment initiation. In none of the cases hemodialysis was performed, although in one case hemodialysis was considered but not executed due to acyclovir-toxicity-related agitation and excessive movement [14]. No acyclovir plasma concentrations were documented in these cases.

In addition to these case reports, Li et al. studied the correlation between dosing on ABW or AdjBW and the risk of AKI in a retrospective cohort study of 94 critically ill adults who received high-dose IV acyclovir (10 mg/kg q8h). The authors concluded that obese patients on a high-dose IV acyclovir did not appear to be at higher risk of nephrotoxicity, regardless of the body-weight type used for acyclovir dosing calculation [18]. However, this short report of a retrospective cohort study did not include any detailed patient characteristics; hence, indication bias (i.e. the choice of using AdjBW instead of ABW) might have had a great impact on these results. In contrast, a recent retrospective case-control study identified obesity as an independent risk factor for acyclovir-induced AKI in patients receiving a median IV dose of 10 mg/kg (odds ratio 3.2; 95% confidence interval 1.19–8.67) [19].

In our patient, the causality of acyclovir-induced AKI and neurotoxicity were assessed and categorized as 'likely' according to the WHO-UMC causality scale [20]. Renal and neurotoxicity are well-described adverse drug effects of acyclovir [1,2]. Furthermore, the time relationship between acyclovir administration and the sudden onset of AKI and audiovisual hallucinations substantiated the causality. Renal function recovered, and hallucinations disappeared as soon as acyclovir plasma concentration decreased due to hemodialysis. There was no plausible alternative explanation for the renal and neurotoxicity in our patient. However, hypovolemia cannot be ruled out as a contributive factor for the supratherapeutic acyclovir concentration.

Recommendations to dose IV acyclovir in obese patients using IBW instead of ABW are not substantiated by pharmacokinetic validation. One case report described the pharmacokinetics in an obese patient treated with 9.4 mg/kg q8h dosed on ABW and renal impairment (creatinine clearance (CLCr) estimated by the Cockcroft–Gault equation, 55 mL/min). In that patient, acyclovir plasma concentrations were measured on day 19 of treatment; the maximal plasma concentration of 43 mg/L (C_{max}) and trough level 16.1 mg/L (C_{8h}) far exceeded concentrations seen in non-obese patients dosed with 10 mg/kg q8h (C_{max} 20.7 mg/L ± 10.2 mg/L; C_{8h} 2.3 mg/L ± 1.4 mg/L). The author concludes that dosing according to IBW or AdjBW would have been expected to reproduce acyclovir exposure seen in non-obese healthy volunteers given 10 mg/kg q8h Smith et al. [17].

In addition, Turner et al. performed a prospective study to examine the pharmacokinetics of IV acyclovir in morbidly obese patients with a BMI > 40 kg/m^2. In this study, the exposure ($AUC_{0-\infty}$) to a 5 mg/kg dose of IV acyclovir in seven morbidly obese patients dosed on IBW was compared with seven normal weight patients (BMI < 25 kg/m^2) dosed on ABW. The acyclovir exposure in obese patients dosed on IBW was substantially lower compared to the exposure in normal-weight patients dosed on ABW (15.2 mg*h/L ± 2.9 vs 24.0 mg*h/L ± 9.4; $p = 0.011$). The authors suggest that dosing based on to AdjBW instead of IBW in obese patients is likely to reach similar exposure as in non-obese patients dosed according to ABW. To date, dosing using AdjBW has not been clinically studied [21].

Prevention and management of acyclovir toxicity

In our patient, the acyclovir dose would have been 720 mg q8h based on AdjBW, 500 mg q8h based on LBW and 570 q8h based on IBW (instead of the administered 950 mg q8h based on ABW). Retrospectively, we would have recommended a starting dose based on AdjBW. The limited literature indicates that dosing acyclovir using ABW in obese patients is likely to result in a higher risk of supratherapeutic drug levels, intratubular crystal nephropathy and neurotoxicity, while dosing on IBW or LBW may lead to undertreatment which should be avoided given the severity of the treated infection. Our case shows that early symptoms of acyclovir toxicity can develop within 24 hours after initiation of the treatment, while laboratory results have a turnaround time that may cause a delay. Therefore, we would emphasize the importance of direct monitoring of urinary output and symptoms associated with neurotoxicity (e.g. confusion, agitation, restlessness and hallucinations) [2]. For early detection, clinicians should be aware that acyclovir toxicity can mimic the signs and symptoms of neurological viral infections. In addition, we recommend daily measurement of renal function and measurement of acyclovir trough plasma concentration 48–72 hours after initiation of the high-dose acyclovir treatment. If acyclovir trough levels are supratherapeutic on a dosage based on AdjBW, the dosage can be further decreased based on IBW.

Although haloperidol admission did not show sufficient effect in treating the neurotoxicity in our patient, previous reports suggest some clinical effectiveness of haloperidol. Successful treatment however required both administration of 2 mg bid haloperidol and subsequently discontinuation of the antiviral agent. Cessation and removal of the drug seem to be the most effective treatment of acyclovir related neurotoxicity, as our patient only showed neurological improvement after hemodialysis due to the lack of acyclovir clearance [22–24]. Lastly, implementation of a clinical rule in electronic health record systems signalling obese (BMI > 30 kg/m^2) patients who are treated with high-dose intravenous acyclovir may be useful to assist clinicians in the detection and prevention of acyclovir overtreatment in obese patients.

Conclusion

By adding this case to the current literature, we would like to enhance awareness among healthcare professionals about adjusted dosing of acyclovir in obese patients to reduce the risk of acyclovir overdosing. Although more research on safe and effective dosing in obese patients is required, we consider a starting dose based on AdjBW instead of ABW as appropriate for obese patients (BMI > 30 kg/m^2) while monitoring closely for clinical efficacy and toxicity. Early-stage therapeutic drug monitoring can be used to further adjust the dosage if necessary, thereby minimizing the risk of developing acyclovir toxicity while preventing undertreatment. Clinical decision support in electronic prescribing systems may contribute to the reduction of patient harm due to overdosing.

CRediT authorship contribution statement

Bastiaan Sallevelt: Conceptualization, Investigation, Writing - original draft, Visualization. **Erin Smeijsters:** Conceptualization, Investigation, Writing - original draft. **Toine Egberts:** Writing - review & editing, Supervision. **Kim van der Elst:** Investigation, Writing - review & editing, Supervision. **Tania Mudrikova:** Conceptualization, Writing - review & editing, Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Patient consent

Obtained.

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