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Incidence, patterns, risk factors and clinical outcomes of intravenous acyclovir induced nephrotoxicity

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ABSTRACT

Objectives: Acyclovir is approved to treat herpes simplex virus (HSV) type 1, type 2 and varicella-zoster virus. It is mainly eliminated via the kidneys, for which drug crystals accumulation might lead to nephrotoxicity. This study aimed to determine the incidence, risk factors, preventive measures, and clinical outcomes of acyclovir induced-nephrotoxicity.
Methods: This is a retrospective cohort study of patients >12 years of age at Sultan Qaboos University Hospital (SQUH) receiving IV acyclovir therapy between January 2016 and December 2020.
Results: Out of 191 included patients, 40 (20.1%) developed acyclovir induced-nephrotoxicity. Age (per year older: OR 1.04, 95 %CI 1.01–1.07), total duration of treatment (per day OR1.19, 95 %CI 1.06–1.33), and concomitant use of vancomycin (OR 5.96, 95 %CI 1.87–19.01) were significant independent risk factors for acyclovir induced-nephrotoxicity development. Nine patients (4.5%) died during the same hospitalization, including those three patients who required renal replacement therapy (1.5%).
Conclusion: Frequent monitoring of kidney function for older patients with concurrent use of vancomycin and IV hydration is essential to prevent IV acyclovir induced-nephrotoxicity. Antimicrobial stewardship is a crucial method to reduce the duration of treatment with IV acyclovir as appropriate.

1. Introduction

Acyclovir was approved to treat herpes simplex virus (HSV) in 1982 (Barber et al., 2019). It is a purine nucleoside synthetic agonist that converts to an active metabolite called acyclovir triphosphate that exhibits antiviral activity against HSV type 1, HSV type 2 and varicella-zoster virus (Kłysik et al., 2020, Cortesi and Esposito, 2008). The primary route of elimination is via the kidneys through glomerular filtration and renal tubular secretion, with a half-life in the body ranging from 2 to 3 h and up to 20 h depending on renal function (Cortesi and Esposito, 2008, Dubrofsky et al., 2016). Renal intratubular deposition of acyclovir crystals or acyclovir direct tubular toxicity are major mechanisms behind nephrotoxicity in patients treated with intravenous (IV) acyclovir (Chang et al., 2016, Izzedine et al., 2005, Yildiz et al., 2013). Unlike IV acyclovir, oral acyclovir is not associated with an increased risk of nephrotoxicity (Lam et al., 2013). After the introduction of acyclovir into the clinical practice, acyclovir induced nephrotoxicity has been reported in 10–48% of the patients; however, in more recent years, the incidence has decreased to 18–21%, which might be linked to dose adjustment, adequate hydration and slow acyclovir infusion (Richelsen et al., 2018). Pre-existing renal disease, obesity and hypertension were associated with an increased risk of acyclovir induced nephrotoxicity (Ryan et al., 2018, Barber et al., 2019, Richelsen et al., 2018, Lee et al., 2018, Yildiz et al., 2013). Also, prolonged duration of treatment concomitant use of nephrotoxic medications is associated with increased risk of acyclovir induced

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nephrotoxicity (Yalcinkaya et al., 2021). Improving intravenous hydration is a protective measure against acyclovir induced nephrotoxicity (Dubrofsky et al., 2016).

Studies from the Middle Eastern Region addressing acyclovir induced nephrotoxicity are spare. Therefore, this study aims to assess the incidence, risk factors, preventive measures, and clinical outcomes of acyclovir induced nephrotoxicity at the largest tertiary centre in Oman.

2. Methodology

2.1. Study design and setting

This retrospective cohort study included all adult patients admitted to Sultan Qaboos University Hospital (SQUH) between January 1st 2016, and December 31st 2020 and treated with IV acyclovir for ≥24 h. We included all admitted adults patients of age ≥12 years old. In contrast, we excluded patients younger than 12 years, patients with haematological or solid organ malignancies, patients on renal replacement therapy, and patients lacking follow up data. Patients with malignancies were not included due to the complexity of diseases, prolonged admissions, and the presence of several other potential causes for nephrotoxicity.

The study was approved by the Medical Ethics Committee of the College of Medicine and Health Sciences at SQUH (REF. NO. SQU-EC/318/2020 MREC #2339).

2.2. Data collection

The following variables were collected: demographic data (age, sex, weight, and height); information on the indication for acyclovir; relevant comorbidities (diabetes mellitus, hypertension, heart failure, and chronic kidney disease (CKD)); information on IV hydration; information on dose and duration of IV acyclovir treatment; concomitant use of relevant medications including non-steroidal anti-inflammatory drugs (NSAIDs), diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers (ARBs), vancomycin, or aminoglycoside; information on the use of contrast medium; creatinine measurements (at baseline before starting acyclovir therapy, at the peak after and during the acyclovir therapy, and latest reading prior to hospital discharge); data on acyclovir induced-nephrotoxicity and clinical outcome (need for renal replacement therapy or death).

2.3. Definitions

Acyclovir dosage regimen was calculated based on mg/kg/dose (ranging from 5 −10 mg/kg/ dose every 8 to 24 h depending on patient creatinine clearance expressed in ml/minutes/1.73 m^2), to be infused over 1 h while maintaining adequate hydration of the patient.

Primary outcome is the incidence of AKI due to acyclovir treatment. Acute kidney injury (AKI)/acyclovir induced-nephrotoxicity and CKD were defined according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (Levey et al., 2005, Khwaja, 2012). which include an increase in serum creatinine ≥26.5 μmol/l within 48 h or 50% from baseline or urine output less than 0.5 mL/kg/h for 6 h. However, due to a lack of data on urine output, we used the serum creatinine level to define acyclovir induced nephrotoxicity.

2.4. Microbiological definitions

Presumed meningoencephalitis: patient presented with symptoms and signs likely caused meningoencephalitis in the absence of other explanation. Lumbar puncture was not obtained due to the presence of contraindication or due to lack of consent.

HSV encephalitis: HSV encephalitis was confirmed using polymerase chain reaction (PCR) of cerebrospinal fluid analysis.

Varicella-zoster infection: diagnosed with the presence of fever and the typical dermatological manifestation of chickenpox or shingles.

2.5. Statistical analyses

Categorical variables were reported as numbers and percentages. Continuous variables were expressed as mean ± SD if normally distributed or median (IQR) if non-normally distributed. Continuous variables (e.g. age, the dose of acyclovir) between the two groups were compared using the student *t*-test for normally distributed variables or Wilcoxon rank-sum for not normally distributed variables. Chi-square test or Fisher's exact were used to assess the association between categorical variables as appropriate. Variables with a p-value < 0.25 on univariate were included in the multivariable logistic regression analysis. Statistical calculations were performed using the Stata v. 16.1 software package (StataCorp).

3. Results

One hundred ninety-nine patients met our inclusion criteria. The mean age was 45.8 ± 19.7 years, and 49.8% were men. The most common comorbidities were hypertension (33.2%), diabetes mellitus (24.1%), CKD (13.9%), and heart failure (6.0%). Presumed meningoencephalitis was the most common indication (87.5%) for IV acyclovir. The average treatment duration was 5.0 ± 4.0 days, and most of the patients (80.9%) received IV hydration. The most common concurrent medications were NSAIDs (29.6%) and vancomycin (28.6%). IV contrast medium was received by 41.2% during the same hospital admission (Table 1).

In total, 40 patients (20.1%) developed acyclovir induced-nephrotoxicity. Univariate analysis revealed that age (p = 0.028), diabetes mellitus (p = 0.027), concurrent use of vancomycin (p = 0.003), aminoglycoside (p = 0.043), higher baseline creatinine value (p = 0.010), and death (p < 0.001) were significantly higher in the acyclovir induced-nephrotoxicity group (Table 1). While multivariate regression analysis showed that only age, total treatment duration, and concomitant vancomycin use sustained significant independent risk factors for acyclovir induced-nephrotoxicity development (Table 2).

Renal replacement therapy was required by three patients (1.5%), and nine patients (4.5%) died during the same hospitalization, including all those who required renal replacement therapy.

4. Discussion

We found that the incidence of acyclovir induced nephrotoxicity in hospitalized patients who received acyclovir was 20.1% which is similar to some of the previously reported studies (Lee et al., 2018, Kim and Byun, 2015, Ryan et al., 2018, Pacheco et al., 2005). Older age, longer duration of treatment, and concomitant vancomycin use were independent risk factors for AKI development. This is the first-time age has been associated with acyclovir induced-nephrotoxicity development. Three patients required renal replacement therapy, and they died during the same hospitalization. Overall, mortality was higher in the acyclovir induced-nephrotoxicity group.

Acyclovir is an effective therapeutic agent for herpes simplex and varicella-zoster viruses infections. Around 60–90% of acyclovir is excreted unmetabolized via the kidneys, for which drug crystal-

Table 1
Demographic, clinical and laboratory data and health outcomes of patients treated with IV acyclovir.

Characteristic, *n (%) unless specified otherwise*	Total cohort (n = 199)	Non- acyclovir induced-nephrotoxicity group (n = 159)	Acyclovir induced-nephrotoxicity group (n = 40)	P-value
Age (year ± SD)	45.8 ± 19.7	44.2 ± 20.1	51.9 ± 16.6	0.028
Male	99 (49.8)	79 (49.7)	20 (50%)	1.000
Weight (kg ± SD)	70.1 ± 21.6	69.0 ± 22.3	76.1 ± 17.8	0.104
Height (cm ± SD)	157.2 ± 16.7	157.3 ± 17.5	156.9 ± 12.6	0.9350
Diabetes mellitus	48 (24.1)	33(20.8)	15 (37.5)	0.027
Hypertension	66 (33.2)	48(30.2)	18 (45.0)	0.058
CKD	29 (13.9)	21 (13.2)	8 (20.0)	0.220
Heart failure	12 (6.0)	8 (5.0)	4 (10.0)	0.220
Presumed meningoencephalitis	133 (87.5)	98 (61.7)	35 (87.5)	0.23
HSV encephalitis	28 (14.1)	26 (16.4)	2(5.0)	0.07
Other HSV infection	1 (0.5)	1 (0.63)	0	
Varicella-zoster infection	37 (18.6)	34 (21.4)	3 (7.5%)	0.06
Total dosage (mg, IQR)	6750 (3750–12400)	7000 (3750–12,400)	5530 (3750–11,900)	0.9376
Total duration of treatment (days ± SD)	5.0 ± 4.1	4.6 ± 3.7	6.4 ± 5.2	0.0577
IV hydration	161 (80.9%)	130 (81.8)	31 (77.5)	0.540
Vancomycin	57(28.6)	38 (23.9)	19 (47.5)	0.003
Aminoglycoside	3 (1.5)	1 (0.6)	2 (5.0)	0.043
Diuretics	31 (15.6)	21 (13.2)	10 (25.0)	0.066
ACEI/ARB	30 (15.1)	24 (15.1)	6 (15.0)	0.988
NSAIDs	59 (29.6)	47 (29.6)	12 (30.0)	0.957
Contrast media	82 (41.2)	64 (40.3)	18 (45)	0.585
Baseline creatinine value (umol/L, IQR)	74 (52–93)	68 (51–87)	82 (52–113)	0.0101
Requirement for renal replacement therapy	3 (1.5)	0 (0)	3 (7.5)	0.001
Death	9 (4.5)	0 (0)	9 (22.5)	<0.001

SD, standard deviation; IQR, interquartile range; CKD: chronic kidney disease; HSV: herpes simplex virus; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; NSAIDs: non-steroidal anti-inflammatory drug.

lization in renal tubules causes tubular obstruction, ischemia and necrosis (Lee et al., 2018). Also, acyclovir aldehyde metabolite may cause direct renal tubular insult leading to acyclovir induced renal toxicity (Whitley et al., 1982). Isotonic hydration has been shown to decrease the risk of IV acyclovir induced renal toxicity (Kim and Byun, 2015, Dubrofsky et al., 2016, Pacheco et al., 2005, Whitley et al., 1982). However, we could not find this in the present study, probably since the great majority had been given IV hydration. This almost certainly reflects the awareness that IV hydration prevents acyclovir nephrotoxicity. Concomitant vancomycin usage and duration of treatment were independent risk factors for acyclovir induced-nephrotoxicity. Hence antimicrobial stewardship is an essential step to avoid unnecessary coadministration of acyclovir and vancomycin and to shorten the duration of acyclovir as clinically appropriate (Barber et al., 2019).

Older age was an additional independent risk factor for acyclovir induced-nephrotoxicity, which could be related to the higher bioavailability of acyclovir due to age-related decreased lean body mass (McLachlan and Pont, 2012) and reduced glomerular filtration rate (GFR) (Catalano and Conforto, 2005, Sagawa et al., 2014). As mentioned previously, this is a novel finding of the current study. Although acyclovir was investigated in children, higher mean age was significantly correlated with acyclovir induced-nephrotoxicity (Yalçinkaya et al., 2021).

CKD is a significant risk factor for acyclovir induced-nephrotoxicity (Lee et al., 2018). However, we could not demonstrate this association in our cohort due to the few CKD patients.

Table 2
Multi-regression analysis of risk factors for developing IV acyclovir nephrotoxicity.

Variables	OR	P-value	95% CI
Age (year)	1.04	0.024	1.01–1.07
Weight (kg)	1.02	0.172	0.99–1.04
Diabetes mellitus	1.49	0.562	0.39–5.70
Hypertension	0.98	0.981	0.26–3.79
Heart failure	0.44	0.515	0.039–5.10
Duration of treatment (days)	1.19	0.003	1.06–1.33
Vancomycin	5.96	0.003	1.87–19.01
Diuretic use	0.34	0.175	0.07–1.62
Baseline creatinine value	1.00	0.375	0.99–1.00

Previous studies have identified other risk factors for acyclovir induced nephrotoxicity, including hypertension, obesity, diabetes mellitus, concomitant use of NSAIDs, ceftriaxone and ACEI (Ryan et al., 2018, Barber et al., 2019, Richelsen et al., 2018, Lee et al., 2018, Yildiz et al., 2013). These differences in reported risk factors may be explained by different patients' types, sample sizes, and renal dysfunction definition (Lee et al., 2018).

Our study has several strengths, including including all relevant data representing risk factors for acyclovir induced-nephrotoxicity and then analyzing them in a multi-regression model to exclude potential confounders. We defined AKI and CKD according to widely recognized and validated criteria, i.e., KDIGO criteria. More importantly, this is the first study to identify age as an independent risk factor for acyclovir induced-nephrotoxicity. However, this study has also several limitations, including the retrospective design, which may compromise the data accuracy. Also, data on urine output, one of the KDIGO criteria to define acyclovir induced-nephrotoxicity, was not gathered. Hence, the incidence may be underestimated. In addition, data on the underlying cause of death were not available.

5. Conclusion

The incidence of acyclovirinduced-nephrotoxicity was around 20%. Older age, longer duration of treatment and containment use of vancomycin were significantly associated with increased acyclovir induced-nephrotoxicity risk. Kidney function monitoring and hydration are essential elements for patients receiving IV acyclovir. Antimicrobial stewardship is an essential step to avoid unnecessary coadministration of acyclovir and vancomycin and to shorten the duration of acyclovir as clinically appropriate.

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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.

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