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(CASE REPORT)

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Severe acyclovir induced neurotoxicity in an elderly woman with end-stage renal disease and herpes zoster : A case report

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Abstract

Acyclovir (ACV) is a widely utilized antiviral medication for treating herpes simplex virus, cytomegalovirus, and varicella-zoster virus (VZV). Despite its usefulness, ACV can lead to adverse effects like acute renal impairment. ACV is predominantly eliminated through the kidneys, and in cases of renal impairment, there exists a potential for elevated levels, posing a risk of subsequent neurotoxicity. This case highlights the challenges posed by ACV use in patients with compromised renal function. A 64-year-old female presented with unconsciousness persisting for several hours. She had recently self-administered acyclovir (5x800 mg) to manage a herpes zoster outbreak. She had history of Chronic Kidney Disease (CKD) Stage V but refused hemodialysis. She had irregular heart rate of 140-180 beats per minute (with EKG confirming Atrial Fibrillation Rapid Response), a respiratory rate of 26 breaths per minute. Other vital sign was stable. Physical examination identified herpes zoster lesions on the right abdomen. Laboratory results shown blood urea nitrogen of 266 mg/dL, creatinine 13.2 mg/dL, and potassium of 6.9 mmol/L . A month earlier, the level of blood urea nitrogen was 100 mg/dL and creatinine was 7.9 mg/dL, indicating a progressive deterioration in renal function. Given the severity of the patient's condition, hemodialysis was initiated. Over the course of five days, there was a notable improvement in both the patient's clinical condition and level of consciousness.

Keywords: Acyclovir; End-Stage Renal Disease; Neurotoxicity; Herpes Zoster; Altered Mental Status

1. Introduction

Acyclovir, a nucleoside analogue, is currently utilized to hinder the replication of various viruses such as herpes simplex virus, cytomegalovirus, and varicella-zoster virus (VZV). In the United States, an overwhelming 99.5% of individuals aged over 40 have encountered VZV infection, resulting in reactivation and the onset of zoster, with an estimated incidence of 1 million cases. The frequency of VZV cases has been progressively increasing, likely contributing to a surge in prescriptions for acyclovir.[1]

Acyclovir, identified chemically as 9-((2-hydroxyethoxy)methyl)guanine (ACV), stands out as a widely utilized antiviral medication belonging to the guanine nucleoside analog class. Its widespread use globally marks the inception of a new era in antiviral therapy, attributed to its remarkable selectivity and minimal cytotoxicity.[2,3] ACV, a widely used antiviral drug, is crucial for global healthcare. Its cost-effective synthesis is vital for development. Despite its success against herpes, ACV can lead to adverse effects like acute renal impairment. The State Drug Administration of China, in April 2009, stressed careful monitoring for signs of renal failure during ACV therapy. Dosing considerations apply, especially for the elderly, pregnant women, and children. Detecting ACV levels is essential due to its toxicological effects. Various analytical methods, applied to pharmaceuticals and human samples, contribute to safe ACV use.[2] The drug's widespread distribution throughout the body, including its ability to penetrate the cerebrospinal fluid, is attributed to its high volume of distribution. ACV is predominantly eliminated through the kidneys, and in cases of renal impairment, there

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exists a potential for elevated levels, posing a risk of subsequent neurotoxicity. Therefore, caution is advised when administering acyclovir to individuals with compromised kidney function.[1] This case highlights the challenges posed by ACV use in patients with compromised renal function.

2. Case Report

A 64-year-old female presented to the Emergency Department with a chief complaint of unconsciousness persisting for several hours. The patient had recently self-administered acyclovir (5x800 mg) to manage a herpes zoster outbreak. Despite a known history of Chronic Kidney Disease (CKD) Stage V, the patient refused hemodialysis. Upon arrival at the Emergency Department, vital signs revealed a blood pressure of 120/70 mmHg, an irregular heart rate of 140-180 beats per minute (with EKG confirming Atrial Fibrillation Rapid Response), a respiratory rate of 26 breaths per minute, body temperature of 36.8 degrees Celsius, and oxygen saturation of 96% on room air. Physical examination identified herpes zoster lesions on the right abdomen, an irregular heart rate, and delirium (Glasgow Coma Scale 10). Laboratory results indicated hemoglobin levels of 11.0 g/dL, leukocytes 7520 µL, platelets 100,000 µL, blood urea nitrogen 266 mg/dL, creatinine 13.2 mg/dL, sodium 148 mmol/L, potassium 6.9 mmol/L, and random glucose of 128 mg/dL. A month earlier, the patient's laboratory results showed blood urea nitrogen of 100 mg/dL and creatinine of 7.9 mg/dL, indicating a progressive deterioration in renal function. Given the severity of the patient's condition, hemodialysis was initiated. Over the course of five days, there was a notable improvement in both the patient's clinical condition and level of consciousness.

3. Discussion

This case raises awareness of the potential complications associated with acyclovir use, particularly in patients with renal impairment. The decision to proceed with hemodialysis proved instrumental in resolving acyclovir-induced delirium, emphasizing the importance of prompt and tailored interventions in such cases.

Acyclovir is predominantly eliminated in its unchanged form through urine, although a minor fraction undergoes metabolism to acyclovir aldehyde. Findings from an in vitro investigation propose that the acyclovir aldehyde metabolite may induce direct harm to renal tubular cells.[4] Acyclovir exhibits widespread distribution in bodily fluids and undergoes elimination via both glomerular filtration and tubular secretion.[5] Only a modest portion, approximately 10% to 30%, of acyclovir is absorbed following oral administration. A substantial majority, ranging from 60% to 90%, undergoes excretion by the kidneys through a combination of glomerular filtration and tubular secretion. The half-life of acyclovir is brief, lasting 2 to 3 hours in individuals with normal kidney function but extending to 20 hours in patients with End-Stage Renal Disease (ESRD). Its protein binding falls within the 9% to 33% range. The drug demonstrates widespread distribution throughout body fluids, with particularly high concentrations observed in the kidney (100%), cerebrospinal fluid (50%), breast milk (324%), and amniotic fluid and placenta (300% to 600%).[5]

In this case, the patient suffers from End-stage renal disease (ESRD). ESRD significantly exacerbates acyclovir-induced neurotoxicity through the intricate interplay of impaired kidney function and altered drug metabolism. In individuals with ESRD, the diminished renal clearance capacity results in the accumulation of acyclovir and its neurotoxic metabolite, 9-carboxymethoxymethylguanine (CMMG), in the systemic circulation. The altered pharmacokinetics of acyclovir, including an extended half-life, further contributes to prolonged drug exposure. This accumulation of acyclovir and its metabolites in the body, particularly in the central nervous system, heightens the risk of neurotoxic effects.

Neurotoxicity induced by acyclovir arises due to the buildup of acyclovir and its metabolite, 9-carboxymethoxymethylguanine (CMMG). It is prevalent, particularly in elderly individuals with compromised renal function, and is marked by a blend of confusion and psychiatric alterations. Additionally, occurrences of seizures, myoclonus, and dysarthria may manifest in affected individuals.[6] In this case, neurotoxicity is characterized by the presence of delirium in the patient. The symptoms of delirium, along with irregular blood pressure, herpes zoster lesions, and laboratory values indicating elevated blood urea and creatinine, suggest potential neurotoxic effects associated with the use of acyclovir. The utilization of acyclovir and related compounds, such as valacyclovir and ganciclovir, poses challenges, particularly in individuals with end-stage renal disease, as their diminished capacity to excrete the drug increases the risk of drug toxicity.[5] This susceptibility to toxicity may manifest as changes in mental status and encephalopathy, affecting patients with acute or chronic kidney disease not undergoing dialysis, those on hemodialysis, peritoneal dialysis, or individuals who have undergone kidney transplantation.[7,8,9] From a clinical standpoint, neurotoxicity induced by ACV often exhibits similarities with encephalitis associated with herpes. Emergency physicians may encounter difficulties in distinguishing between these conditions and may grapple with the

decision of whether to continue the medication. Both herpes-associated encephalitis and ACV-induced neurotoxicity can manifest as subtle alterations in conscious level, encompassing a spectrum from delirium to coma.[10]

Elevated levels of the primary acyclovir metabolite, 9-carboxymethoxymethylguanine (CMMG), in either serum or cerebrospinal fluid (CSF) serve as strong indicators of acyclovir-induced neurotoxicity.[11] A study examining CMMG serum levels demonstrated that receiver-operating characteristics curve analysis yielded a sensitivity of 91% and specificity of 93% in predicting the onset of neuropsychiatric symptoms.[12]

Because of its low molecular weight, minimal protein binding, limited volume of distribution (0.6 L/kg), and pronounced water solubility, acyclovir stands as a favorable candidate for elimination through hemodialysis. The utilization of peritoneal dialysis has also been employed in addressing acyclovir toxicity, and certain experts recommend enhancing this modality for more effective drug removal. For dialysis patients experiencing neurotoxicity, hemodialysis is the preferred treatment method due to its superior removal rate compared to peritoneal dialysis, although the latter can also achieve some degree of acyclovir removal.[5,13] Urgent hemodialysis serves as a swift method to reduce plasma ACV levels, it has the capacity to swiftly restore renal function and consciousness levels within a few hours. To sum up, the challenge of promptly diagnosing instances of ACV neurotoxicity underscores the necessity for a readily available and specific diagnostic tool in all emergency departments (EDs). Urgent hemodialysis emerges as a crucial instrument for the early identification and management of ACV neurotoxicity.[10]

4. Conclusion

Acyclovir-induced neurotoxicity in the context of ESRD presents a complex clinical scenario. This case report underscores the necessity of careful consideration of medication choices in patients with renal compromise and the effectiveness of hemodialysis in managing acyclovir-related complications.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from patient included in the study.

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