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Case Report

# Zonisamide-induced acute kidney injury

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## 1. Introduction

Zonisamide is a new generation anticonvulsant indicated for the adjunctive management of partial seizures in adults [1]. The anticonvulsant activity of zonisamide is predominantly related to the inhibition of voltage-gated sodium action potentials and reduction of T-type calcium-channel currents. Because of its broad mechanism of action, zonisamide is used for many types of epilepsy and in patients whose epilepsy is resistant to other antiepileptic drugs (AEDs) [2,3]. There is insufficient evidence to demonstrate the superior clinical effectiveness of zonisamide compared to other adjunctive AEDs; however, its long half-life of 63 h supports convenient once- or twice-daily dosing. In vitro studies have demonstrated antioxidant and neuroprotective properties at therapeutic doses, suggesting that zonisamide may protect against ischemic damage and recurrent seizure activity [4].

Therapy is generally well tolerated; the most common reported adverse events include somnolence in 17% of patients and dizziness and anorexia in 13% of patients. Zonisamide may be an alternative in some patients over agents associated with weight gain, such as valproate or pregabalin [5,6]. Zonisamide is metabolized by acetylation to *N*-acetyl zonisamide and reduction to 2-sulfamoylacetyl phenol (SMAP) by cytochrome P450 isoenzyme 3A4. Zonisamide primarily undergoes renal excretion with 62% recovered from urine and 3% from feces following multiple doses [1,7].

The package insert was recently updated to reflect a risk of hyperchloremic, nonanion gap metabolic acidosis due to weak inhibition of carbonic anhydrase and increased renal excretion of bicarbonate. Furthermore, according to the manufacturer's label, zonisamide is not recommended for use in patients with renal failure (defined by the manufacturer as an estimated GFR < 50 mL/min); use of this agent in patients with renal insufficiency, defined as having a GFR < 60 mL/min according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative, requires slower titration and more frequent clinical monitoring for toxicities and adverse effects. Avoidance of use of zonisamide in individuals with end-stage kidney disease (e.g., GFR < 15 mL/min or on dialysis) is prudent based on manufacturer recommendations. Zonisamide has been associated with a statistically significant 8% mean increase in serum creatinine and blood urea nitrogen in clinical trials; however, this effect dissipated after therapy was discontinued. Of note, a case report has demonstrated hypersensitivity syndrome with acute kidney injury due to zonisamide; however; acute kidney injury has not been previously reported as an adverse event of zonisamide [7]. We present a case report

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that suggests that such an association exists as demonstrated by acute kidney injury in a patient on two separate occasions.

## 2. Case report

A 33-year-old Caucasian man was admitted to the emergency department following status epilepticus and loss of consciousness. His medical history included mental retardation, hypertension, hemiplegia, and partial-onset epilepsy. The patient had no history of smoking, alcohol abuse, or known drug allergies. Home medications included phenytoin 100 mg in the morning and 200 mg before sleep, zonisamide 200 mg daily, loratadine 10 mg daily, naltrexone 50 mg daily, and propranolol extended release 120 mg daily. The patient received lorazepam 2 mg for seizure management and was intubated for airway protection. Physical examination on presentation showed normal heart rate and blood pressure and a slightly elevated temperature of 100.2 °F. Laboratory testing included a serum creatinine level of 1.2 mg/dL (reference range: 0.5–1.2 mg/dL), blood urea nitrogen level (BUN) of 12 mg/dL (16–23 mg/dL), lactate level of 2.9 mmol/L (0.5–2.2 mmol/L), total phenytoin level of 6.9 μg/mL (10–20 μg/mL), and albumin level of 4.3 g/dL (3.5–5 g/dL). Upon consultation with the epileptologist, the patient was loaded with intravenous phenytoin 1000 mg.

Zonisamide was increased to a regimen of 200 mg–100 mg–200 mg daily, and phenytoin was subsequently maintained at usual doses. On day 2, he was extubated without complications. Urinalysis revealed 2 + protein and 1 + blood. Laboratory testing demonstrated an elevated creatinine phosphokinase (CPK) level of 542 U/L (25–150 U/L), serum creatinine level of 2.8 mg/dL, and BUN level of 23 mg/dL. Zonisamide was discontinued on day 3 because of continued evidence of intrinsic kidney injury including a $FE_{Na}$ of 2.6. The total phenytoin concentration had increased to 23.5 μg/mL, and lacosamide 50 mg twice daily was initiated for adjunctive management. The patient's course was complicated by fevers and a left lower lobe infiltrate treated empirically with intravenous piperacillin/tazobactam 4.5 g every 8 h. This regimen was maintained until day 6, at which point serum creatinine level was 1.3 mg/dL, BUN level was 12 mg/dL, and both lungs were clear. The patient was discharged on a three-day regimen of levofloxacin 500 mg, previous doses of phenytoin, and lacosamide 50 mg twice daily to be increased to three times daily after one week.

Of note, our patient was restarted on zonisamide as outpatient after the first admission and before the second admission for reasons unknown to the medical team. The patient was admitted to the emergency department ten months later with a similar presentation of status epilepticus, loss of consciousness, and a fever of 102.8 °F. The patient was managed with two doses of lorazepam 2 mg IV and intubated for airway protection. Regular medications were unchanged from the previous admission with the exception of increased zonisamide dosing of 100 mg–100 mg–200 mg daily. Labs of note upon admission included serum creatinine level of 0.9 mg/dL, BUN level of 11 mg/dL, and total phenytoin level of 10.5 μg/mL. It was suspected that the breakthrough seizures were due to a compilation of missed doses and an infectious cause. Broad-spectrum empiric antibiotics were started, including one dose of ceftriaxone 2 g, vancomycin 1 g every 12 h, and piperacillin/tazobactam 4.5 g every 8 h. Doses of antiepileptic drugs were increased; on day 2, the patient received zonisamide 200 mg three times daily and phenytoin 125 mg twice daily. Labs later that day revealed an elevated serum creatinine level of 4.7 mg/dL, BUN level of 49 mg/dL, and CPK level of 4410 U/L. The patient was producing concentrated, tea-colored urine at approximately 0.13 mL/kg/h. Differential diagnosis of acute myocardial infarction, Wegener's granulomatosis, and systemic lupus erythematosus was ruled out through creatinine kinase MB, DNA, myeloperoxidase, and serine protease 3 antibodies and ANA-titer studies.

The concern for acute kidney injury due to zonisamide was such that it was discontinued, and the patient required one session of hemodialysis on day 3 in conjunction with intravenous fluid hydration. Levetiracetam was initiated at 250 mg twice daily. An ultrasound of the kidneys demonstrated right-sided perinephritis. Urinalysis results were similar to the first visit, including 1 + protein, 2 + blood, and 1 + ketone bodies. Kidney function was monitored closely, and subsequent dialysis sessions were not needed. The patient was extubated to a nasal cannula on day 3. Subsequent complications included pulmonary infiltrates and edema evident on chest X-ray on day 8 for which the patient received levofloxacin 750 mg every 48 h. Therapy for pneumonia was de-escalated on day 10 to azithromycin 500 mg and ceftriaxone 1 g daily. The patient received empiric piperacillin/tazobactam 4.5 g every 8 h on days 12 through 15 for fever of unknown origin. Pan cultures throughout the hospitalization remained negative. The patient was discharged on day 18 upon resolution of acute kidney injury; at discharge, serum creatinine level was 1.1 mg/dL and BUN level was 9 mg/dL. Antiepileptic therapy was changed to phenytoin 100 mg three times daily and levetiracetam 500 mg twice daily because of concern that zonisamide had been the cause of acute kidney injury.

## 3. Discussion

There is only one previously published case report of acute kidney injury occurring with zonisamide. A 29-year-old Japanese man presented to the hospital with acute kidney injury requiring dialysis secondary to drug-induced hypersensitivity syndrome two months after initiation of zonisamide [7]. According to the package insert, impaired renal function (defined by the manufacturer as a creatinine clearance < 20 mL/min) is associated with decreased zonisamide clearance. Data from several studies demonstrate an 8% mean increase in serum creatinine and BUN from baseline; however, there were no reports of acute kidney injury [1]. Discontinuation of zonisamide is recommended in patients who develop acute renal failure or experience a significant increase in serum creatinine or BUN [2].

Zonisamide is thought to be the cause of acute renal failure in this patient because of the temporal relationship demonstrated on two separate hospital admissions. Baseline kidney function was within normal range at both admissions and drastically worsened after zonisamide was increased. Concomitant medications were reviewed by the intensivists, epileptologist, clinical pharmacist, and nephrologists and were ruled out for possible drug-induced acute kidney injury. The results of the urinalysis and $FE_{Na}$ indicate intrinsic renal failure. The detrimental effects from up-titration of zonisamide were likely perpetuated by volume depletion and rhabdomyolysis from seizure activity. A positive myoglobin and the rapid increase in serum creatinine on both admissions are consistent with muscle injury secondary to seizure activity, zonisamide, or a combination of the two.

The likelihood of zonisamide causing acute renal failure in this patient was found to be probable based on the Naranjo Adverse Drug Reaction Probability Scale [8]. Elevated CPK concentration could have resulted from rhabdomyolysis secondary to seizure activity; however, there have been postmarketing reports of rhabdomyolysis in patients taking zonisamide indicating it may be a sequela of the drug itself [2]. Clinicians should be aware of this potential adverse event and should closely monitor kidney function in patients being started on, or receiving increased doses of, zonisamide. Furthermore, this case speaks to the importance of accurate medication reconciliation procedures in ensuring safe continuation of therapy. Patients are often poor historians, but medical records may provide valuable information regarding pharmacotherapy. In this case, the evidence of acute kidney injury on the first admission should have served to caution against subsequent use and up-titration.

## Conflict of interest

None of the authors contributing to this paper report any financial disclosures or conflicts of interest.

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