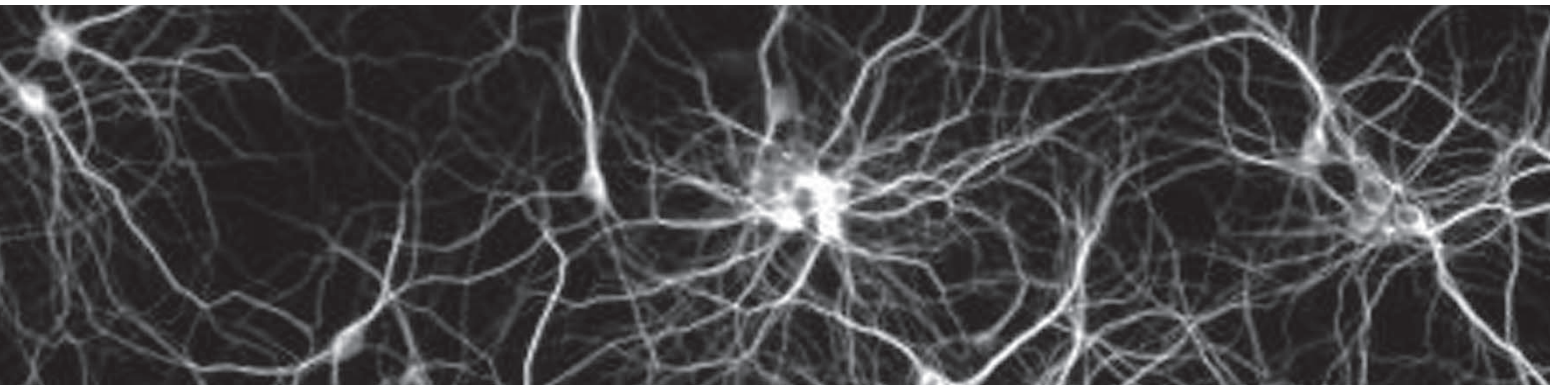

Acute renal insufficiency caused by zonisamide treatment

Zurap Raifi[1], Berislav Ruška[1], Gordana Sičaja[1], Ana Sruk[1]

ABSTRACT – *Objective*: To inform about possible renal damage caused by zonisamide treatment. *Case description*: We present a case of a 69-year-old female with newly diagnosed focal epilepsy, in whom the therapy with zonisamide caused acute renal insufficiency. *Results*: After initiation of zonisamide in therapy, the patient developed signs of renal failure, which resolved after zonisamide therapy cessation. *Conclusion*: One should be aware of possible renal damage as a side effect of zonisamide.

Keywords: antiseizure medication, renal insufficiency, zonisamide

INTRODUCTION

Zonisamide is a sulfonamide drug that can be used to treat various types of (epileptic) seizures, although it is most commonly used for the treatment of focal epilepsy (1). The most common side effects of zonisamide include cognitive and psychiatric impairments, as well as weight loss (2). Here we present a rare case of acute renal insufficiency caused by treatment with zonisamide in a patient with focal epilepsy.

CASE REPORT

In 2019, a female patient, who was at the time 69 years old, reported to the neurologist with a history of episodes that resembled focal seizures with sensory onset and impaired awareness. The patient described that in such episodes she initially feels tingling in a small finger of her left hand, which then spreads to other fingers and the lateral side of the left forearm. Soon after, she becomes puzzled, oblivious, and responds inadequately. Usually, after around 15 to 20 minutes, such episodes resolve spontaneously. Two such episodes happened in 2017 and one in 2018. The patient suffered from hypertension, type 2 diabetes, hyperlipidemia, and osteopenia years prior. On the workup, electroencephalography (EEG) showed no epileptiform activity, carotid ultrasound showed no hemodynamic abnormalities, and her brain magnetic resonance imaging (MRI) showed

[1] Department of Neurology, Sveti Duh University Hospital, Zagreb, Croatia

extensive chronic cerebrovascular changes with cortical atrophy. Initially, the patient was not keen to start antiseizure medication (ASM) since she had already been taking eight other drugs for her other medical conditions. However, around a year later, in the first half of 2020, she had another seizure similar to the ones previously described, so it had been decided to start treatment with zonisamide. We gradually increased the dose by 100 mg every two weeks, ultimately reaching a daily dose of 300 mg. Soon after reaching the target dose, she began to experience symptoms such as nausea with occasional vomiting, infrequent loose stools, weight loss, and oliguria. Her blood test showed elevated levels of serum creatinine (457 μmol/L, ref. value 49-90 μmol/L) and urea (15.7 mmol/L, ref. value 2,8-8,3 mmol/L), which indicated acute renal insufficiency. She was hospitalized at the nephrology department, and fluid replacement therapy was started. Kidney ultrasound showed no abnormalities. Drug toxicity was suspected, so zonisamide dose had been slowly reduced. A series of laboratory findings thereafter showed a gradual recovery of kidney function. Nephrologists concluded that zonisamide was the cause of acute renal insufficiency, and deemed the kidney biopsy unnecessary. Zonisamide had been replaced with lamotrigine, and the patient had been discharged from the hospital. In the follow-up control examinations, the patient was feeling well, and her epilepsy was well controlled with lamotrigine. Laboratory findings during control intervals showed satisfactory renal recovery with residual chronic renal impairment, which has not progressed further.

DISCUSSION

In this paper, we present a case of acute renal insufficiency caused by zonisamide. Although nephrolithiasis as a possible adverse event of zonisamide has been previously debated (2), renal failure as another possible side effect is not commonly known. We found only two previous reports of zonisamide related zonisamide-related renal injury by searching the literature. The first was described in a 29-year-old Japanese male (3). However, in that case, kidneys were one of many organs that were damaged indirectly due to the drug-induced hypersensitivity syndrome phenomenon. The second report was in a 33-year-old American male, where renal failure was directly associated with zonisamide (4). In our case, renal failure was also firmly time-related to zonisamide treatment, while all of the other possible causes were excluded by the treating nephrologist. If we consider that together with the aforementioned case, we can confidently conclude that there is a direct correlation between the two. The pathophysiological mechanism that could explain this phenomenon is speculative. However, it might be associated with the drug's sulfonamide structure and its effect of inhibition of carbonic anhydrase. As mentioned earlier, the formation of kidney stones has already been described as an adverse effect of chronic use of zonisamide, but it has long been known as an adverse effect of chronic use of sulfonamides in general (2,5). Moreover, the effect of sulfonamide urine crystal precipitation could be aggravated by the effect of zonisamide's carbonic anhydrase inhibition, leading to alkalinisation of urine. Even though this adverse effect happens during chronic drug use, it has been described in other sulfonamides that sulfonamide crystals in some cases, especially in acute exposure, can precipitate intratubular and cause an intratubular obstruction, which leads to retrograde urine flow, and therefore, anuric kidney injury (5,6). Previously described cases of acute renal failure caused by acetazolamide, which shares the same sulfonamide structure, and the effect of carbonic anhydrase inhibition with zonisamide, support this theory (6). After all, it is important to mention that our patient was probably more prone to kidney injury due to a long history of hypertension and diabetes. This case report, together with one previously described, supports the fact that zonisamide can cause renal impairment and that clinicians should be aware of it when introducing this antiseizure drug into therapy. It is important, however, to keep in mind the limitations of single case reports and their lack of generalizability, therefore further research is necessary to confirm this observed adverse effect and its clinical importance.

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Address for correspondence: Berislav Ruška, MD; E-mail: berislav.ruska@gmail.com