Distal renal tubular acidosis and lethargy associated with zonisamide treatment in a dog with idiopathic epilepsy

Takamasa Itoi1,2 | Natsuki Akashi1,2 | Yuki Shimizu1 | Keisuke Sugimoto1,2 | Akihisa Hata2 | Kenji Kutara1,2 | Takako Shimokawa Miyama1,2 | Teppei Kanda1,2

1Veterinary Medical Teaching Hospital, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Japan
2Department of Veterinary Medicine, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Japan

Correspondence
Teppei Kanda, Department of Veterinary Medicine, Faculty of Veterinary Medicine, Okayama University of Science, Imabari, Ehime 794–8555, Japan.
E-mail: t-kanda@ous.ac.jp

Abstract
A 3-year-old neutered male golden retriever administered zonisamide for the treatment of seizures showed lethargy and had normal anion gap metabolic acidosis with hypokalaemia, hyperchloremia, and alkaline urine. The serum zonisamide concentration was close to the upper limit, which raised a suspicion of adverse effects of zonisamide. This is the first report showing that the fractional excretion of bicarbonate after compensation for the plasma bicarbonate concentration by a sodium bicarbonate infusion was approximately 5%, indicating distal renal tubular acidosis (RTA). The serum zonisamide concentration decreased, and adverse effects were abated by reducing the zonisamide dosage. Diagnostic therapy with bicarbonate served as a means of compensating for bicarbonate deficiency and contributed to the clinical diagnosis of the condition in zonisamide-associated RTA in dogs.

KEYWORDS
bicarbonate, dog, fractional excretion, renal tubular acidosis, zonisamide

1 | INTRODUCTION
Zonisamide is a second-generation antiepileptic drug that was first approved approximately two decades ago for humans and has also been widely used in recent small animal practice for the treatment of seizures associated with epilepsy. The most commonly reported adverse effects in dogs include sedation, ataxia, vomiting, loss of appetite, and suppression of thyroid hormone synthesis (Boothe & Perkins, 2008; Chung et al., 2012; Dewey et al., 2004; von Klopmann et al., 2007). Although its frequency may be fairly rare, zonisamide can cause an adverse effect of distal renal tubular acidosis (RTA) as reported in a human patient (Inoue et al., 2000). Similar idiosyncratic adverse effect has been demonstrated previously in a canine case (Cook et al., 2011). However, limited information has been published in veterinary practice. Here, we report a clinical case and laboratory findings of distal RTA associated with zonisamide in a dog.

2 | CASE DESCRIPTION
A 3-year-old neutered male golden retriever weighing 30.5 kg (body condition score 5/9) was presented to a primary care veterinary hospital with tonic-spasm seizures and was treated with zonisamide (6.6 mg/kg, PO, BID; Zonisamide tablet 100 mg ‘Amel’, Kyowa Pharmaceutical Industry Co., Ltd, Osaka, Japan) after having two seizures in 3 weeks. The dog had no relevant medical history. The dog was brought to the veterinary hospital for further examination and imaging tests because seizure frequency did not decrease despite prolonged administration of zonisamide for 3 months, and staggering and falling
occurred. The dog had experienced a total of 13 seizures, all of which lasted 2 or 3 min.

On the first day in the hospital (day 0), the dog presented with lethargy and anorexia. The dog was lying face down as soon as it entered the examination room and tended to be somnolent at rest. A gait test showed an unsteady when walking. Vital signs included normothermia (39.2°C, rectal temperature), a pulse rate of 77 beats/min, and a respiratory rate of 40 breaths/min or panting. Systolic, mean, and diastolic blood pressures obtained by oscillometric measurements were 107, 87, and 67 mm Hg, respectively. Echocardiography revealed both low fractional shortening and bradycardia (60–70 beats/min). Neurological examination revealed a slight decrease in proprioception in the bilateral forelimbs and a decrease in the bilateral hindlimbs. The results of thoracic and hip joint radiography were unremarkable. Abdominal radiography and ultrasonography indicated no morphological abnormalities in the kidneys or other organs. Plasma biochemical analyses indicated notable findings including hypokalaemia (potassium concentration, 3.62 mEq/L; reference range, 3.8–5.0 mEq/L) and hyperchloremia (chloride concentration, 121.1 mEq/L; reference range, 102.0–117.0 mEq/L). Sodium (151.7 mEq/L; reference range, 141–152 mEq/L) and magnesium (1.9 mg/dl; reference range, 1.8–2.4 mg/dl) levels were within the normal ranges. Blood urea nitrogen and creatinine levels were 20.6 mg/dl (reference range, 9.2–29.2 mg/dl) and 0.96 mg/dl (reference range, 0.4–1.4 mg/dl), respectively. The biochemical analysis results also revealed decreased total bilirubin (0.07 mg/dl; reference range, 0.1–0.50 mg/dl), gamma glutamyl transferase (3.0 U/L; reference range, 5.0–14.0 U/L), and ammonia concentrations (11.6 µg/dl; reference range, 16.0–75.0 µg/dl). A complete blood count was performed, and the findings were unremarkable. Arterial blood gas analysis revealed borderline acidemia (pH 7.37; reference range, 7.35–7.45), low bicarbonate concentration (10.7 mEq/L; reference range, 18.8–25.6 mEq/L), low base excess (<0.2), and urine was negative for glucose according to a dipstick test. Urinary tract infection was ruled out because urinary sediment findings were negative for erythrocytes, leukocytes, and microbes. Considering the dog's history and the aforementioned results, RTA attributed to zonisamide was strongly suspected. On this day, the serum zonisamide concentration of 38.6 µg/dl was close to the upper limit, although within the recommended therapeutic range (10–40 µg/dl), and this concentration is the value obtained at 15 h after the last dose. The zonisamide dose was reduced to 3 mg/kg, PO, BID. Scheduled computed tomography and magnetic resonance imaging under anaesthesia were postponed because of acid-base balance abnormalities.

In the next follow-up examination (day 17), the gait became lighter and stronger without wobbling. The dog remained lethargic although became more active at home and more willing to walk. The frequency of seizures did not increase. The heart rate (108 beats/min) and systolic blood pressure (154 mmHg) were elevated compared with those at the previous visit. Neurological examination revealed an improvement in proprioception in the extremities, which returned to normal. At that time, the serum zonisamide concentration showed a decrease to 15.1 µg/ml. The plasma sodium, potassium, and chloride concentrations were 147.5, 3.88, and 118.5 mEq/L, respectively. Arterial blood gas analysis revealed a normal pH (7.38), arterial PO2 of 117.0 mm Hg, and PCO2 of 24.0 mm Hg with a low bicarbonate concentration of 13.8 mEq/L, and the urine pH was 7.80 (glass electrode meter). We considered that the prolonged lethargy was somewhat attributable to the underlying acidosis. Hence, primarily to clarify responsiveness of bicarbonate compensation to lethargy, and secondary to distinguish the RTA types, sodium bicarbonate was administered. As there is a risk of alkalosis as a result of the bicarbonate loading test, venous blood gas, urine pH, urine bicarbonate concentration, and urine PCO2 were carefully monitored using a benchtop analyzer (GASTAT-720; Techno Medica Co., Ltd, Yokohama, Japan). After emptying the bladder via a urinary catheter, infusion of sodium bicarbonate (Meylon Injection 8.4%, Otsuka Pharmaceutical Factory Inc., Naruto, Japan) was initiated at 0.5 mEq/kg/h. Urine samples were collected via a urinary catheter every 20 min, and venous blood was anaerobically sampled from a saphenous vein at each midpoint of the aforementioned 20 min. Every 40 min, the infusion rate was stepwise doubled if the monitored venous and urine pH were confirmed to not drastically change. A sodium bicarbonate infusion was administered at 0.5 mEq/kg/h for the first 40 min, 1.0 mEq/kg/h for the next 40 min, and 2.0 mEq/kg/h for the final 20 min; it was then discontinued because venous bicarbonate recovered to normal (venous bicarbonate, 19.4 mEq/L). As the sodium bicarbonate infusion rate increased, both bicarbonate concentrations and PCO2 in venous blood and urine gradually became elevated, but the fractional excretion (FE) of bicarbonate was still <5%, except for those given at 2.0 mEq/kg/h (Figure 1, Table 1). The dog became more active immediately after bicarbonate compensation and was less lethargic for approximately 3 days thereafter.

On the next follow-up (day 28), the dog's gait and activity were improved compared with the previous visit (day 17). Plasma sodium, potassium, and chloride concentrations were all within the normal ranges (145.5, 4.35, and 112.6 mEq/L, respectively). Mild hyperventilation was still present (arterial PO2 and PCO2 were 111.4 and 26.7 mm Hg, respectively) although arterial bicarbonate (20.3 mEq/L) and base excess (<4.4 mEq/L) had returned to normal. Plasma symmetric dimethylarginine concentrations were measured using preserved samples (stored at −80°C) on days 0, 17, and 28 to clarify background kidney disease; although the result was temporarily high on day 0 (15 µg/dl; reference range, 0–14 µg/dl), it was considered unremarkable because these values were sustained within the normal range on days 17 (11 µg/dl) and 28 (10 µg/dl). Although lethargy and
Venous blood bicarbonate concentrations and urine fractional excretion (FE) of bicarbonate before (baseline) and during a bicarbonate loading test with sodium bicarbonate infusion at 0.5, 1.0, and 2.0 mEq/kg/h in a dog with renal tubular acidosis attributed to zonisamide treatment.

**FIGURE 1**

| Variable          | Baseline | 0.5  | 1.0  | 2.0  |
|-------------------|----------|------|------|------|
| Venous blood pH   | 7.35     | 7.36 | 7.39 | 7.35 |
| PO₂ (mm Hg)       | 65.1     | 36.6 | 24.8 | 23.5 |
| PCO₂ (mm Hg)      | 26.1     | 26.3 | 29.1 | 35.9 |
| Base excess (mEq/L)| −11.6   | −11.1| −7.7 | −6.0 |
| Haemoglobin (mg/dL)| 14.2    | 13.8 | 13.3 | 12.8 |
| Creatinine (mg/dL)| 1.05     | 1.07 | 1.05 | 1.03 |
| Sodium (mEq/L)    | 147.5    | 146.8| 147.3| 150.7|
| Potassium (mEq/L) | 3.88     | 4.03 | 4.17 | 4.23 |
| Chloride (mEq/L)  | 118.5    | 118.5| 118.3| 119.6|
| Urine pH          | 7.71     | 7.60 | 7.87 | 7.94 |
| PCO₂ (mm Hg)      | 70.4     | 33.8 | 65.6 | 76.9 |
| Bicarbonate (mEq/L)| 94.8   | 35.6 | 116.4| 158.9|
| Specific gravity  | 1.036    | 1.038| 1.039| 1.035|
| Creatinine (mg/dL)| 158     | 156  | 148  | 111 |
| Sodium (mEq/L)    | 323      | 240  | 364  | 385 |
| Potassium (mEq/L) | 143     | 155  | 108  | 84 |
| Chloride (mEq/L)  | 201     | 218  | 217  | 196 |
| Fractional excretion (%) | 1.45 | 1.12 | 1.75 | 2.36 |
| Sodium            | 24.4     | 26.5 | 18.3 | 18.5 |
| Potassium         | 1.12     | 1.26 | 1.30 | 1.52 |

Note: PO₂, oxygen partial pressure; PCO₂, carbon dioxide partial pressure.

**TABLE 1**

*DISCUSSION*

The present report showed an acid-base imbalance characterized by RTA in a dog administered zonisamide for epilepsy treatment, even though the blood concentrations were within the therapeutic range. A distal RTA associated with zonisamide was first recognized in a human child patient (Inoue et al., 2000). Similar idiosyncratic adverse effect has been demonstrated previously in a canine case that exhibited hyperchloremic, normal anion gap metabolic acidosis with hypokalaemia, and mildly alkalinized urine (pH > 6.5) (Cook et al., 2011), which was consistent with the acid-base balance changes that occurred in our case. The dog in a previous report (Cook et al., 2011) showed borderline alkalemia due to accompanying primary respiratory alkalosis caused by hyperventilation, probably owing to the psychological anxiety effect of zonisamide. Hyperventilation with reduced arterial PCO₂ beyond normal respiratory compensation was compatible with that in our present report. However, the arterial blood pH in the current case might not have changed significantly because of the interaction between metabolic acidosis and respiratory alkalosis and therefore appeared to be within the normal range.

The mechanisms of RTA caused by zonisamide were not addressed in this report. Zonisamide may suppress the propagation of epileptogenic activity by blocking voltage-dependent sodium and T-type calcium channels, inhibiting both dopaminergic and serotonergic pathways, and/or potentiating gamma-aminobutyric acid activity in the central neuron system (Biton, 2007). The drug structure contains a sulphonamide side chain resembling acetazolamide, which weakly inhibits the carbonic anhydrase effect (De Simone et al., 2005; Masuda & Karasawa, 1993). The acetazolamide-like action of zonisamide has been suggested to affect pathways involved in proton secretion via bicarbonate reclamation in the distal tubules of the kidney, resulting in the presence of distal RTA (Inoue et al., 2000). Otherwise, distal RTA may occur congenitally or could be associated with renal failure (DiBartola, 2012; Martinez & Hostutler, 2014; Nicoletta & Schwartz, 2004; Torrente et al., 2019). The history of the dog and the uneventful results of blood chemistry (blood urea nitrogen, creatinine, and symmetric dimethylarginine) and ultrasonography of the kidneys suggested that these abnormal conditions were not involved in the current case.

The present report is the first to show FE of bicarbonate in a dog with zonisamide-associated RTA after sodium bicarbonate administration. The gold standard for the diagnosis of distal RTA is a confirmation of urine pH > 6.0 after an ammonia chloride loading test (DiBartola, 2012). The diagnosis of distal RTA can also be confirmed with a bicarbonate loading test, as the FE of bicarbonate is < 5% for the distal type metabolic acidosis were nearly resolved, the seizures still occurred with unchanged frequency. To investigate the primary disease causing the seizures, computed tomography and magnetic resonance imaging were performed on this day with the initial purpose for which the dog came to the hospital. As a result, there were no specific findings in the whole body; therefore, we diagnosed that the seizures were caused by idiopathic epilepsy.
and >15% for the proximal type at normal plasma bicarbonate concentration increased by sodium bicarbonate administration (DiBartola, 2012). In the human case of zonisamide-associated RTA (Inoue et al., 2000), impairment of renal acidification was confirmed by an ammonia chloride loading test; it was diagnosed based on the results of a bicarbonate loading test, which showed uneventful FE of bicarbonate (approximately 6%). In a previous report of zonisamide-associated RTA, bicarbonate loading test was conducted, although the results were inadequate to reach the conclusion of the RTA type, as the post-urine pH of 5.5 was the boundary between the distal and proximal types. In the current report, proximal RTA can be ruled out, and distal RTA is suggested, as they were around 5% before and after compensating plasma bicarbonate concentration to the normal level.

Although the results of the bicarbonate loading test indicated distal RTA in this case, the FE of bicarbonate during a sodium bicarbonate infusion at 2.0 mEq/kg/h was above 5%, which was not within the criteria for distal RTA. One possible reason is that the increased rate of blood bicarbonate concentration in the present case (3.36 mEq/L/h in total) was extensively high above the recommended rates for diagnostic purposes, for which sodium bicarbonate should have been administered to increase the serum bicarbonate concentration by 0.5 to 1 mEq/L/h for distinguishing between RTA types (Polzin et al., 1986). Such a high dosing rate might have led to excess body fluid, resulting in osmotic diuresis enough to affect the increase in FE of bicarbonate; an increase in plasma sodium level and FE of sodium with decreased haemoglobin concentration at this dose rate compared to those at baseline could support this idea. On the other hand, it cannot be completely denied that bicarbonate reabsorption was slightly reduced in the proximal tubule, resulting in a combined proximal and distal RTA. A limitation of our present report is our inability to evaluate the proximal tubular function as a transport maximum mechanism of bicarbonate; therefore, further investigation is needed to elucidate a more detailed mechanism.

4 CONCLUSION

In conclusion, this report described lethargy and distal RTA induced by zonisamide, which characterized as normal anion gap metabolic acidosis with alkaline urine, and first to show the FE of bicarbonate in a dog with zonisamide-associated RTA. These findings indicated the importance of continuous urinalysis in epilepsy cases treated with zonisamide to detect acid-base imbalance. Our results also implied that diagnostic therapy with bicarbonate served as a means of compensating for bicarbonate deficiency and contributed to the clinical diagnosis of the condition in zonisamide-associated RTA in dogs.

ACKNOWLEDGEMENT

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Formal analysis (lead), investigation (equal), resources (equal), writing—original draft preparation (equal), and writing—review and editing (equal): Takamasa ITOI. Formal analysis (equal), investigation (equal), methodology (lead), writing—original draft preparation (equal), and writing—review and editing (equal): Yuki Shimizu. Investigation (equal) and writing—review and editing (equal): Keisuke Sugimoto. Investigation (equal) and writing—review and editing (equal): Akihisa Hata. Investigation (equal) and writing—review and editing (equal): Kenji Kutara. Investigation (equal) and writing—review and editing (equal): Takako Shimokawa Miyama. Conceptualization (lead), project administration (lead), supervision (lead), and writing—review and editing (equal): Teppei Kanda.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal’s author guidelines page. This report is on owner-owned dogs, so the consent of the owner has been obtained in treatment and publication.

DATA AVAILABILITY STATEMENT

Research data are not shared.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.905.

ORCID

Natsuki Akashi https://orcid.org/0000-0002-8294-0607
Yuki Shimizu https://orcid.org/0000-0002-8961-6447
Keisuke Sugimoto https://orcid.org/0000-0002-7565-4960
Teppei Kanda https://orcid.org/0000-0002-7103-3462

REFERENCES

Biton, V. (2007). Clinical pharmacology and mechanism of action of zonisamide. Clinical Neuropharmacol, 30, 230–240.
Boothe, D. M., & Perkins, J. (2008). Disposition and safety of zonisamide after intravenous and oral single dose and oral multiple dosing in normal hound dogs. Journal of Veterinary Pharmacology and Therapeutics, 31, 544–553.
Chung, J., Hwang, C., Chae, J., Ahn, J., Kim, T., Seo, K., Lee, S., & Youn, H. (2012). Zonisamide monotherapy for idiopathic epilepsy in dogs. New Zealand Veterinary Journal, 60, 357–359.
Cook, A. K., Allen, A. K., Espinosa, D., & Barr, J. (2011). Renal tubular acidosis associated with zonisamide therapy in a dog. Journal of Veterinary Internal Medicine, 25, 1454–1457.
De Simone, G., Di Fiore, A., Menchise, V., Pedone, C., Antel, J., Casini, A., Scozzafava, A., Wurl, M., & Supuran, C. T. (2005). Carbonic anhydrase inhibitors. Zonisamide is an effective inhibitor of the cytosolic isozyme II and mitochondrial isozyme V. Solution and X-ray crystallographic studies. Bioorganic & Medicinal Chemistry Letters, 15, 2315–2320.
Dewey, C. W., Guiliano, R., Boothe, D. M., Berg, J. M., Kortz, G. D., Joseph, R. J., & Budsberg, S. C. (2004). Zonisamide therapy for refractory idiopathic epilepsy in dogs. Journal of the American Animal Hospital Association, 40, 285–291.
DiBartola, S. P. (2012). Metabolic acid-base disorders. In S. P. DiBartola (Ed.), Fluid, electrolyte, and acid-base disorders in small animal practice (4th ed., pp. 253–286). Edwards Brothers Inc.
Inoue, T., Kira, R., Kaku, Y., Ikeda, K., Gondo, K., & Hara, T. (2000). Renal tubular acidosis associated with zonisamide therapy. *Epilepsia*, 41, 1642–1644.

Martinez, S. A., & Hostutler, R. A. (2014). Distal renal tubular acidosis associated with concurrent leptospirosis in a dog. *Journal of the American Animal Hospital Association*, 50, 203–208.

Masuda, Y., & Karasawa, T. (1993). Inhibitory effect of zonisamide on human carbonic anhydrase in vitro. *Arzneimittelforschung*, 43, 416–418.

Nicoletta, J. A., & Schwartz, G. J. (2004). Distal renal tubular acidosis. *Current Opinion in Pediatrics*, 16, 194–198.

Polzin, D. J., Osborne, C. A., & Bell, F. W. (1986). Canine distal renal tubular acidosis and urolithiasis. *Veterinary Clinics: Small Animal Practice*, 16, 241–250.

Torrente, C., Molina, C., Bosch, L., & Costa-Farré, C. (2019). Transient distal renal tubular acidosis in a dog with gastric-dilatation volvulus. *Canadian Veterinary Journal*, 60, 174–178.

von Kloppmann, T., Rambeck, B., & Tipold, A. (2007). Prospective study of zonisamide therapy for refractory idiopathic epilepsy in dogs. *Journal of Small Animal Practice*, 48, 134–138.

How to cite this article: Itoi, T., Akashi, N., Shimizu, Y., Sugimoto, K., Hata, A., Kutara, K., Miyama, T. S., & Kanda, T. (2022). Distal renal tubular acidosis and lethargy associated with zonisamide treatment in a dog with idiopathic epilepsy. *Veterinary Medicine and Science*, 8, 2256–2260. https://doi.org/10.1002/vms3.905