

Toxicity of zoledronic acid after intravenous administration: A retrospective study of 95 dogs

David John Brewer^{1,2}  | Michael Macfarlane^{1,3} | Erin O'Connell² | Nicholas J. Bacon^{1,4}

¹Fitzpatrick Referrals Oncology and Soft Tissue, Surrey, United Kingdom

²Small Animal Teaching Hospital, Leahurst, University of Liverpool, Neston, United Kingdom

³North Downs Specialist Referrals (NDSR), Bletchingley, United Kingdom

⁴University of Surrey School of Veterinary Medicine, Surrey, United Kingdom

Correspondence

David John Brewer, Small Animal Teaching Hospital, Leahurst, University of Liverpool, Neston, CH64 7TE, United Kingdom.
Email: d.brewer@liverpool.ac.uk

Abstract

Background: There is a paucity of veterinary literature on the safety or outcome of zoledronic acid (ZA) use in dogs for either bone pain or hypercalcemia.

Hypothesis/Objectives: The primary aim was to report the adverse events in dogs receiving intravenous administration of ZA.

Animals: Ninety-five dogs with ZA use.

Methods: A retrospective cohort study was performed; all dogs that received at least 1 dose of ZA and had a serum biochemistry profile performed before and after treatment were reviewed. Diagnosis, indication for treatment, adverse events and survival times were recorded.

Results: Ninety-five dogs met the inclusion criteria. Thirty-one (33%) received multiple intravenous infusions of ZA (range, 2-7), making a total of 166 administrations in all dogs. The dose range was 0.13 to 0.32 mg/kg, given at intervals of 4 to 6 weeks. Thirteen adverse events were recorded in 10 dogs: azotemia (n = 8), vomiting (n = 2), pancreatitis (n = 1), cutaneous ulceration (n = 1), and diarrhea (n = 1). Zoledronic acid could not be confirmed as the cause of azotemia in any case. The change in serum creatinine concentration from dose to dose was not related to the total dose received ($P = .46$). Five dogs (5%) changed Veterinary Comparative Oncology Group Common Terminology Criteria (VCOG-CTAE) renal/genitourinary grade after administration of ZA; their total dose 0.4 mg/kg (range, 0.26-0.66) was not significantly different to the group which did not change VCOG-CTAE renal/genitourinary grade 0.35 mg/kg (range, 0.2-1.50; $P = .93$).

Conclusions and Clinical Importance: Multiple doses of ZA were well tolerated in dogs within this study. A small number of dogs developed progressive azotemia which was not associated with cumulative dose.

KEYWORDS

bisphosphonate, hypercalcemia, metastatic bone lesions, osteosarcoma, palliative

Abbreviations: BPH, benign prostatic hyperplasia; BUN, blood urea nitrogen; IRIS, International Renal Interest Society; mZA, multiple doses of zoledronic acid; NSAID, nonsteroidal anti-inflammatory drug; VCOG-CTAE, Veterinary Comparative Oncology Group Common Terminology Criteria; ZA, zoledronic acid.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Journal of Veterinary Internal Medicine* published by Wiley Periodicals LLC on behalf of American College of Veterinary Internal Medicine.

1 | INTRODUCTION

Zoledronic acid (ZA) is a member of the bisphosphonate family of drugs, specifically classified as a nitrogen-containing bisphosphonate or aminobisphosphonate. Bisphosphonates are commonly used for the management of osteoporosis in humans.¹ They are effective in the management of both bone pain (ostealgia) and hypercalcemia in dogs.²⁻⁴

Compared to pamidronate, ZA has a greater potency, efficacy and can safely be infused over a shorter administration time to humans.^{5,6} Zoledronic acid is as well tolerated as pamidronate in humans when used to manage metastatic breast cancer and multiple myeloma.^{1,6,7} In human medicine, bisphosphonates are also used to treat hypercalcemia of malignancy by inhibiting bone resorption,¹ typically in patients with multiple myeloma, breast cancer and prostate cancer.⁷⁻⁹ In veterinary medicine, ZA is effective in the treatment of hypercalcemia of malignancy in small number of dogs.²

In humans, the most clinically important adverse effect of ZA is acute renal insufficiency, with an incidence of 10% to 15%.¹⁰ Other common adverse effects are hypophosphatemia, hypokalemia, and hypocalcemia.¹⁰ There is a paucity of data regarding the toxicity of ZA in dogs. Pharmacodynamic and pharmacokinetic data in 20 dogs with malignant osteolysis confirmed ZA was well tolerated.¹¹ The bone metabolic effects of ZA decrease significantly from baseline 21 to 28 days after administration in 4 dogs, using validated bone turnover markers, urine N-telopeptide and serum bone-specific alkaline phosphatase.¹¹ In 9 tumor-bearing dogs, serum blood urea nitrogen (BUN) concentrations increased with cumulative treatment cycles of ZA, at 0.25 mg/kg given over 15 minutes.¹¹ Bisphosphonate related osteonecrosis of the jaw in humans is a complication of cumulative doses of ZA and is reported in 1 dog.^{12,13}

The aim of this retrospective study was to report the toxicoses in dogs receiving ZA in a large referral hospital in the United Kingdom, with a specific focus on nephrotoxicosis. The secondary aims were to report the survival times in a cohort of dogs with cancer (osteosarcoma or bone-destructive neoplasia) that received ZA for palliative analgesia, and to document the change in serum ionized calcium concentration when ZA was used to treat hypercalcemia of malignancy.

2 | MATERIALS AND METHODS

The medical records of Fitzpatrick Referrals Oncology and Soft Tissue Hospital were searched for dogs that had received at least 1 dose of ZA between September 2015 and September 2019. For inclusion the dogs needed to have had serum biochemistry performed within 4 weeks before to the ZA infusion and repeat serum biochemistry preceding subsequent administration(s) (Catalyst Dx Chemistry Analyzer, VetStat Electrolyte Blood Gas Analyser).

The signalment, body weight, primary diagnosis, presence or absence of metastatic disease and clinical indication for receiving ZA were recorded for each case. A diagnosis of neoplasia was considered definitive if there was cytological or histological confirmation from a board-certified clinical or anatomical pathologist. Cases for which neoplasia was only suspected from diagnostic imaging were analyzed as a separate group.

The use of additional anticancer therapies (surgery alone, radiotherapy alone, chemotherapy alone, or a combination of the previous treatments) was recorded, as well as additional analgesia prescribed.

The dose (mg/kg), number of doses given, and cumulative dose of ZA per dog (mg/kg) were recorded. In every case, ZA was diluted in a 100 mL bag of sterile 0.9% saline and administered IV over 15 minutes. The hospital advised a dose at 0.25 mg/kg every 4 weeks based on the previously described literature however dosing was left at the clinician's discretion,^{4,11} Serum urea and creatinine concentration before each administration were recorded. Adverse events that were identified in the clinical history were recorded, including the potential influence of concurrent medication. An azotemic event was defined as an increase in serum creatinine concentration above the upper reference range for the hospital analyzer (1.88 mg/dL). If the starting value of serum creatinine concentration was already greater than this, any further increase was deemed an adverse event. When available, serum ionized calcium concentration before and after administration was recorded (as mg/dL).

Dogs that received more than 1 dose of ZA were further evaluated: multiple doses of ZA group (mZA). This group was divided into 4 groups based on degree of azotemia; no azotemia, mild azotemia, moderate azotemia and severe azotemia, defined according to the Veterinary Comparative Oncology Group Common Terminology Criteria (1-4) for renal adverse events (VCOG-CTAE) grading scheme.¹⁴ This grading scheme uses values defined by the International Renal Interest Society (IRIS) chronic kidney disease staging scheme (Table 1).¹⁵ Group classification was assessed and assigned for each ZA treatment. Dogs were then allocated into 2 further groups:

mZA group 1; dogs that had no change in their degree of azotemia group, or VCOG-CTAE renal/genitourinary grade after ZA treatment(s).

mZA group 2 dogs had a change in their degree of azotemia group and VCOG-CTAE renal/genitourinary grade after ZA treatment(s).

The following outcomes were recorded: time of diagnosis to death (in days), time from first ZA dose to death (in days), cause of death, or the last point of contact if still alive.

2.1 | Statistical analysis

Categorical variables were counted, and proportions used to summarize the data. Continuous variables were reported as medians and ranges because they were not normally distributed. Within the mZA group, logistical regression was used for comparison of 2 continuous variables (Microsoft Excel, Redmond, Washington). A Welch's *T* test was used to compare mZA groups 1 and 2 that had unequal variances and sample size (Prism 9, Graph Pad Software, La Jolla, California).

3 | RESULTS

Zoledronic acid was administered to 110 dogs from September 2015 to September 2019; of these, 15 were excluded because of a lack of

TABLE 1 Summarized table of the assigned baseline azotemia groups within the mZA group, the corresponding VCOG-CTAE renal/genitourinary grade and the corresponding serum creatinine concentration cut-off values within each grade

Assigned baseline azotemia group	VCOG-CTAE renal grading	Creatinine (as per IRIS CKD guidelines)
No azotemia	1—Asymptomatic	<1.4 mg/dL
Mild	2—Mild clinical signs	1.4-2.0 mg/dL
Moderate	3—Transitional clinical signs	2.1-5.0 mg/dL
Marked	4—Uremic	>5.0 mg/dL
N/A	5—Death	Death

Abbreviations: mZA, multiple doses of zoledronic acid; VCOG-CTAE, Veterinary Comparative Oncology Group Common Terminology Criteria.

baseline serum biochemistry. Ninety-five dogs therefore met the inclusion criteria. There were 41 neutered males, 14 intact males, 34 neutered females, and 6 entire females. Thirty-eight different breeds were represented; 12 crossbreeds, 10 Labrador retrievers, 7 greyhounds, 4 rottweilers, and 4 Cocker spaniels; the full list of breeds is provided (Table S1).

The median age at the time of the first administration of ZA was 9 years (range, 1-15 years). The median weight was 32.4 kg (71 lbs; range, 4.3-80 kg; 9.3-176 lbs).

Zoledronic acid was primarily prescribed as analgesia for malignancy in 86 dogs. In 8 dogs, it was used to treat hypercalcemia and in 1 dog for both conditions. Sixty-six (out of 95) dogs received at least 1 concurrent therapy with a total of 50 dogs receiving chemotherapy, 32 dogs undergoing surgery and 8 dogs receiving radiation therapy. All dogs received adjunctive analgesia medication (Table S2). Fifty-four dogs received ZA and a nonsteroidal anti-inflammatory drug medication (NSAID), a potential nephrotoxin. There were 166 administrations of ZA to 95 dogs at 11 dosages; the median dose was of ZA per administration was 0.25 mg/kg ($n = 97$). The remaining doses were given at 0.20 mg/kg ($n = 46$), 0.22 mg/kg ($n = 7$), 0.13 mg/kg ($n = 4$), 0.24 mg/kg ($n = 3$), 0.23 mg/kg ($n = 3$), 0.21 mg/kg ($n = 2$), 0.32 mg/kg ($n = 1$), 0.28 mg/kg ($n = 1$), 0.26 mg/kg ($n = 1$), and 0.17 mg/kg ($n = 1$). Five dogs had dose changes throughout treatment. Four had dose reductions from 0.01 to 0.05 mg/kg. One dog had a dose increase of 0.12 mg/kg for 2 subsequent doses and a dose reduction of 0.05 mg/kg upon final administration.

3.1 | Adverse events

Zoledronic acid was administered a total of 166 times to 95 dogs, with 13/166 (8%) adverse events in 10/95 (11%) dogs. The adverse effects were azotemia ($n = 8$), vomiting ($n = 2$), diarrhea ($n = 1$), pancreatitis ($n = 1$), and cutaneous ulceration ($n = 1$). Sixty-four dogs (67%) received a single dose, and 31 dogs received multiple infusions of ZA (mZA group) with a range of 2 to 7 administrations. Before treatment

with ZA, 74 dogs were classified as no azotemia, 20 mild azotemia and 1 dog moderate azotemia; no dogs had severe azotemia. Eight azotemic events were recorded in 6 dogs during treatment. All 6 dogs had been treated with at least 1 NSAID before development of azotemia. Three of the 6 dogs had an identifiable likely cause for the azotemia: 1 had presumed renal infiltrative neoplasia based on abdominal ultrasound, 1 developed postrenal obstruction/azotemia because of benign prostatic hyperplasia (BPH) and 1 had transient azotemia with a urine specific gravity of 1.037, suggestive of prerenal azotemia. Dogs that developed vomiting, diarrhea, or both, were concurrently receiving medication with known gastrointestinal adverse effects: carboplatin ($n = 2$), meloxicam ($n = 1$), and lomustine ($n = 1$). The exact cause of the vomiting, diarrhea, or both could therefore not be identified. One dog with an appendicular osteosarcoma developed a focal zone of cutaneous ulceration directly over the mass within a week of administration of a single dose of ZA (image 1).

3.2 | Dogs that received mZA group

There were 31 dogs within the mZA group. The change in serum urea and creatinine concentration from the first to the last administration was calculated. The dogs in this group received a median total ZA dose of 0.45 mg/kg (range, 0.20-1.50). The median change in serum urea and creatinine concentration were 3.6 mg/dL (range, -57.6 to 316) and 0.05 mg/dL (range, -0.362 to 2.86), respectively. The change in serum urea ($P = .70$) and creatinine ($P = .46$) from baseline to final serum values in each dog was not related to the total dose of ZA received (Figures 1 and 2).

In the mZA group, 26 dogs were allocated to mZA group 1 (no change in VCOG-CTAE grade) and 5 dogs were allocated to mZA group 2 (change in VCOG-CTAE grade). The total dose of ZA was not statistically different between dogs in mZA group 1 and mZA group 2 ($P = .93$). Twenty-two of the 31 dogs within the mZA groups 1 and 2 were concurrently receiving a NSAID. In mZA group 1, 18 out of 26 dogs were receiving a NSAID; in mZA group 2 grade 4/5 were receiving NSAIDs.

Two dogs within mZA group 2 developed moderate azotemia, consistent with a VCOG-CTAE grade 3 adverse event. One was a 10-year-old male entire rottweiler with a poorly differentiated sinus adenocarcinoma. The dog received palliative therapy with ZA (0.22 mg/kg) and analgesia including paracetamol and meloxicam. The serum creatinine and urea were 3.82 and 405 mg/dL, respectively, at the time of the fourth administration of ZA. This dog developed severe stranguria, abdominal ultrasound confirmed prostatomegaly, cytology was most consistent with benign prostatic hyperplasia. The dog was euthanized because of poor quality of life, 257 days after diagnosis. The other was a 4-year-old female neutered Bernese Mountain dog, which received ZA (0.2 mg/kg) for palliative management of an appendicular histiocytic sarcoma. Urea and creatinine were 190 and 4.42 mg/dL, respectively, at the time of the third administration of ZA. Abdominal ultrasound was suggestive of a neoplastic infiltration presumed to be disease progression. The dog was euthanized 224 days after initial diagnosis.

3.3 | Outcomes of dogs with confirmed neoplasia that received ZA

Of the 95 dogs treated, 72 had definitive diagnoses of: appendicular osteosarcoma ($n = 24$), histiocytic sarcoma ($n = 9$), anal sac adenocarcinoma ($n = 8$), soft tissue sarcoma ($n = 5$), nonappendicular osteosarcoma ($n = 4$), poorly differentiated neoplasm ($n = 4$), squamous cell carcinoma ($n = 3$), fibrosarcoma ($n = 3$), multiple myeloma ($n = 3$), nasal adenocarcinoma ($n = 2$), chondrosarcoma ($n = 2$), melanoma ($n = 2$), prostatic carcinoma ($n = 2$), and parathyroid adenoma ($n = 1$). Twenty-two dogs had a suspected diagnosis of neoplasia based on diagnostic imaging. One dog had hypercalcemia without an identifiable cause. These 23 dogs were excluded from survival analysis. In the 72 dogs with a definitive diagnosis of neoplasia, median time from diagnosis to death was 122 days (range, 1-1264) and the median time from first treatment to death was 111 days (range, 1-1157). Fifty-nine dogs were euthanized, 4 dogs died either in hospital or at home, 7 dogs were lost to follow up, and 1 dog was still alive at last contact (15th February 2021), 1056 days after administration of ZA. There was no indication that any dog died as a direct result of receiving ZA.

Twenty-four dogs had confirmed appendicular osteosarcoma, 13 underwent amputation and 11 of these then had adjunctive single agent carboplatin, 2 received no adjunctive chemotherapy. Of the 11 dogs that did not have amputation, 6 dogs that received ZA alone, and 4 had combined ZA and carboplatin. Nineteen dogs were euthanized, 3 were lost to follow up and 2 dogs died at home. In all 24 dogs, the overall median survival time from diagnosis to death was 131 days (range, 24-614) and from first treatment to death was 128 days (range, 20-520). The dogs that received ZA alone without any other treatment; the median time from diagnosis and first treatment to death was 59 days (range, 34-309) and 52 days (range, 30-306), respectively.

3.4 | Outcomes of dogs that received ZA for hypercalcemia

Zoledronic acid was used to primarily treat hypercalcemia in 9 dogs, 1 of which for hypercalcemia and bone pain. Five were diagnosed with anal sac adenocarcinoma and 1 each with multiple myeloma, cutaneous plasmacytosis and pituitary adenoma. In 1 dog, a diagnosis

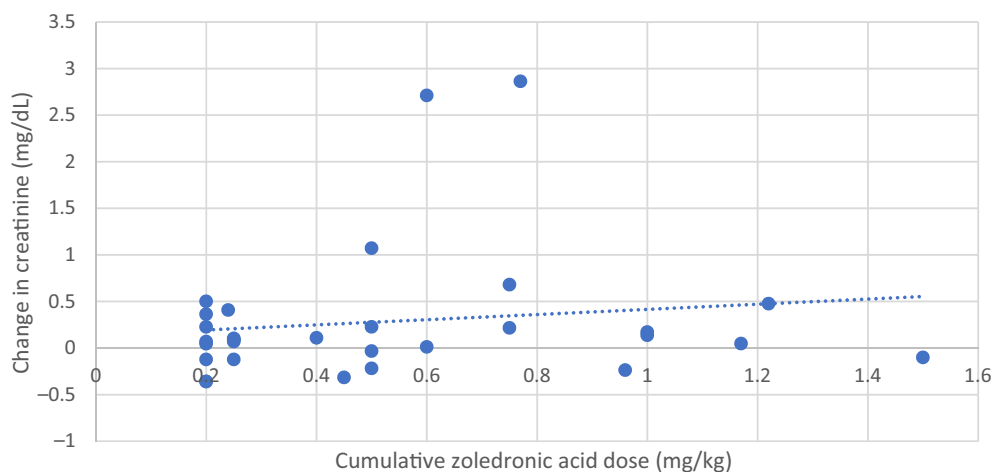


FIGURE 1 Comparison of the cumulative dose of zoledronic acid (mg/kg) to change in serum creatinine concentration over time in dogs that received 2 or more intravenous infusions of zoledronic acid

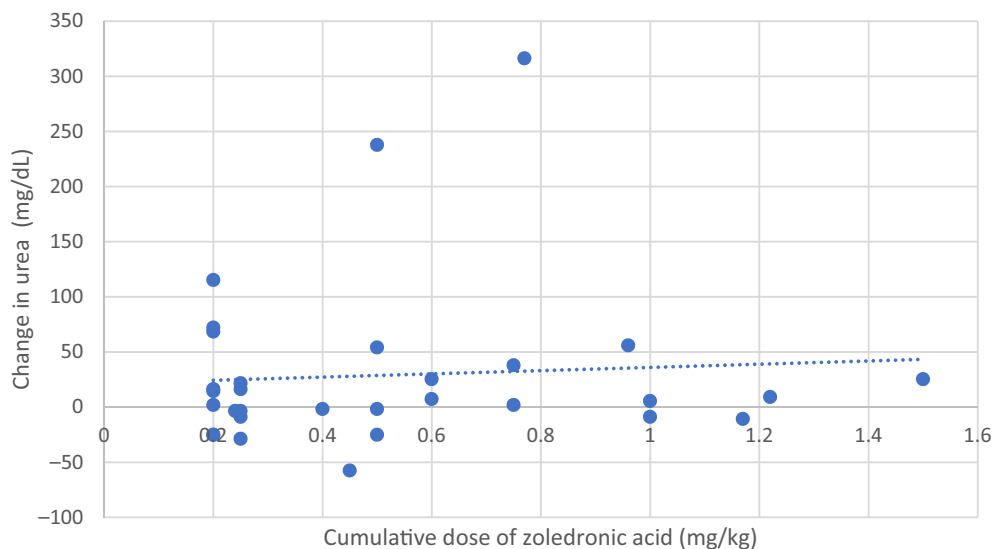


FIGURE 2 Comparison of the cumulative dose of zoledronic acid (mg/kg) to change in serum urea concentration over time in dogs that received 2 or more intravenous infusions of zoledronic acid

of suspected idiopathic hypercalcemia was made after whole-body CT, abdominal ultrasound of the ventral cervical region and abdomen, thoracic limb radiographs, PTH and PTHrP assay with ionized calcium, measurement of 25-hydroxyvitamin D and urinalysis. Measurement of ionized calcium was performed after 24 to 48 hours of ZA administration of ZA. All 9 dogs had an initial decrease in ionized calcium, by a median of 0.40 mmol/L (range, 0.01-0.85). Results for ionized calcium pre- and postadministration of ZA for each dog are shown in Supplemental Figure 1. Ionized calcium normalized in 1 dog (1.40 mmol/L, reference interval 1.25-1.45). Two dogs had no other medical intervention. One dog with primary hyperparathyroidism because of a parathyroid adenoma had a reduction in ionized calcium of 0.68 mmol/L after 1 administration of ZA (0.25 mg/kg). Treatment was given to this dog before subsequent curative parathyroidectomy and on follow up the dog was euthanized 1157 days after ZA because of an unrelated condition. The second dog, a 13-year cocker spaniel with anal sac adenocarcinoma, had a reduction of 0.05 mmol/L after 1 administration of ZA (0.25 mg/kg). It also had surgery and was euthanized because of progressive disease 250 days after administration of ZA.

4 | DISCUSSION

In this retrospective cohort study, we describe the reported incidence of toxicoses, response to therapy and survival times of 95 dogs receiving ZA for ostealgia or hypercalcemia. Zoledronic acid was well tolerated, with 85/95 dogs (89%) having no documented adverse events.

Azotemia was the most common adverse event with 8 individual events of azotemia recorded in 6 dogs. All 6 dogs had also recently received a concurrent NSAID, which are potentially nephrotoxic. Four out of the 5 of dogs within mZA group 2, which changed VCOG-CTAE grade were also concurrently receiving a NSAID with ZA. This finding is consistent with the increased risk of azotemia in people who receive ZA and a NSAID concurrently.¹⁰ In addition, 1 dog potentially had renal neoplasia, and another had obstructive BPH. However, over half the dogs (54) within the study received concurrent NSAIDs in conjunction with ZA. Eighteen of the dogs that were in mZA group 1, these dogs did not change VCOG-CTAE grade. While the exact contribution ZA made to the azotemia cannot be determined, vigilant monitoring with ZA administration in cases with prerenal, renal, or postrenal disease is prudent.

The cutaneous ulceration that occurred in 1 dog might represent dermatotoxicity. In humans, dermatological changes associated with ZA are rare, with only 4 documented dermatological adverse reactions reported; 2 cases of noninterface dermatitis; and 3 cases of interface dermatitis.¹⁶ In the dog described here, the skin was not biopsied to determine the underlying etiology and so the authors are unable to confirm if the histopathology is consistent with ZA dermatotoxicity in humans. The region of necrosis was also overlying a femoral osteosarcoma, and so local ischemia or vasculitis because of the primary tumor is likely.

Bisphosphonate related osteonecrosis of the jaw was not identified as an adverse event in this study. The single previously reported case was a dog that had received multiple treatments over 156 weeks, with a total cumulative dose of ~4.6 mg/kg,¹¹ considerably more than any dog in this study, where the highest cumulative dose in an individual dog was 1.25 mg/kg over 32 weeks. Bisphosphonate related osteonecrosis of the jaw in humans receiving ZA is associated with risk factors such as long-term use, severe periodontal disease, and high cumulative dose.¹³ It is likely the dogs in this study did not receive a high enough dose or for long enough to be at risk for this adverse effect.

In the mZA group of 31 dogs, there was no association between the change in serum creatinine or urea concentration and the cumulative dose of ZA. This is consistent with reports in humans,^{6,10} while a study of a smaller cohort of 9 dogs identified a significant increase in BUN but not creatinine.¹¹ The lack of significant change in our study could be because of the larger cohort size, the number of doses, and the variation in intensity (0.13-0.32 mg/kg) and schedule of doses.

No significant difference was identified in the total dose of ZA received between mZA group 1, those dogs which did not change VCOG-CTAE renal/genitourinary grade compared to mZA group 2, those dogs that did change. It would therefore appear that multiple administrations of ZA do not appreciably increase the risk of azotemia and are well tolerated in most dogs.

Zoledronic acid is effective as sole therapy for the management of hypercalcemia in dogs. All hypercalcemic dogs in this study had an initial decrease in ionized calcium. One dog that had successive treatments for hypercalcemia was well controlled with ZA alone. The duration of and peak response to ZA in hypercalcemic dogs cannot be further elucidated from our data.

A secondary aim of this study was to report the survival time of dogs with a histopathological or cytological diagnosis of neoplasia that received ZA, and specifically those with osteosarcoma. There was a wide range of survival times from diagnosis to death and first dose of ZA to death. This likely reflects the inclusion of a heterogeneous primary tumor type and stage of disease, most of which were receiving treatment for ostealgia and undergoing palliative therapies only. Notably, the median time from diagnosis to death (122 days) and median time from first treatment of ZA to death (111 days) was similar suggesting that receipt of ZA was close to the time of diagnosis in most cases and did not contribute to the cause of acute death. The dogs with a confirmed diagnosis of osteosarcoma that received ZA had substantially shorter survival times with the median survival time of 131 days (range, 24-614) when compared to dogs receiving standard of care treatment (amputation or partial amputation with adjunctive platinum-based chemotherapy) for osteosarcoma, which was reported to be 277 days (range, 203-355).^{17,18} In the authors' opinion, this is likely because of a selection bias for cases with late-stage disease, many of which had amputation declined by the owners. A prospective study investigating dogs receiving ZA as part of a palliative medical treatment protocol where owners have elected against amputation and chemotherapy for appendicular bone cancer is recommended.

The main limitation of this study is its retrospective nature. Inconsistency in recording adverse events, lack of reporting by owners or failure to repeat sufficient serum biochemistries might have led to

under reporting of adverse events. For example, several dogs that received a dose of ZA, with after, but not before treatment measurement of urea and creatinine were excluded from analysis. This might have led to an underreporting of adverse events. Urinalysis was infrequently performed, therefore when azotemia was identified it was not possible to confirm or exclude volume-responsive vs intrinsic change in renal damage. Furthermore, acute renal toxicity could not be assessed with serum biochemistry being performed at 4 weekly intervals rather than within 48 hours as per the IRIS definition of an acute kidney injury.¹⁹

5 | CONCLUSION

Intravenous administration of ZA is well tolerated in dogs with the vast majority of dogs having no reported physical or biochemical adverse effects. Cumulative ZA dosing does not appear to have a direct relationship with increases in serum creatinine and urea concentration. Azotemia was identified with cumulative ZA dosing in a small number of dogs with either concurrent urogenital tract disease or receiving NSAID. Monitoring of serum urea and creatinine is advised, especially where individuals have preexisting azotemia and are receiving concurrent potentially nephrotoxic drugs.

ACKNOWLEDGMENT

No funding was received for this study. All data that supports the findings of this paper are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

ORCID

David John Brewer  <https://orcid.org/0000-0002-0515-8048>

REFERENCES

- Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int*. 2008;19(6):733-759.
- Scheck A, Lux C, Lane J, Martin O. Evaluation of zoledronate as a treatment for hypercalcemia in four dogs. *J Am Anim Hosp Assoc*. 2018;54(6):e54606.
- Spugnini EP, Vincenzi B, Caruso G, et al. Zoledronic acid for the treatment of appendicular osteosarcoma in a dog. *J Small Anim Pract*. 2009;50(1):40-46.
- Lorimier LP. Fan TM bone metabolic effects of single dose zoledronate in healthy dogs. *J Vet Intern Med*. 2005;19(6):924-927.
- Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc*. 2008;83(9):1032-1045.
- Mantyh PW. Bone cancer pain: from mechanism to therapy. *Curr Opin Support Palliat Care*. 2014;8(2):83-90.
- Perry CM, Figgitt DP. Zoledronic acid: a review of its use in patients with metastatic cancer. *Drugs*. 2004;64(11):1197-1211.
- Rosen LS, Gordon D, Kaminski M, et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double blind, comparative trial. *Cancer J*. 2001;7(5):377-387.
- Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease: treatment of newly diagnosed multiple myeloma: an international, double blinded, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol*. 2018;19(3):370-381.
- McDermott RS, Kloth DD, Wang H, et al. Impact of zoledronic acid on renal function in patients with cancer: clinical significance and development of a predictive model. *J Support Oncol*. 2006;4(10):524-529.
- Fan TM, de Lorimier LP, Garrett LD, et al. The bone biologic effects of zoledronate in healthy dogs and dogs with malignant osteolysis. *J Vet Intern Med*. 2008;22:380-387.
- Lundberg AP, Roady PJ, Somrak AJ, et al. Zoledronate-associated osteonecrosis of the jaw in a dog with appendicular osteosarcoma. *J Vet Intern Med*. 2016;30(4):1235-1240.
- Hoff AO, Toth BB, Altundag K, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res*. 2008;23:826-883.
- Veterinary cooperative oncology group—common terminology certain for adverse events (VCOG-CTAE) follow chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. *Vet Comp Oncol*. 2016;14(4):417-446.
- International Renal Interest Society (IRIS). *IRIS Staging of CKD*; 2009. c2007. <http://www.iris-kidney.com/guidelines/staging.html>. Accessed October 18, 2020.
- Succaria F, Collier MC, Mahalingham M. Zoledronic acid induced interface dermatitis. *Am J Dermatopathol*. 2015;37(12):933-993.
- Saam DE, Liptak JM, Stalker MJ, et al. Predictors of outcome in dogs treated with adjuvant carboplatin for appendicular osteosarcoma: 65 cases (1996-2006). *J Am Vet Med Assoc*. 2011;238(2):195-206.
- Endo-Munoz L, Bennett TC, Topkas E, et al. Auranofin improves overall survival when combined with standard of care in a pilot involving dogs with osteosarcoma. *Vet Comp Oncol*. 2020;18(2):206-214.
- International Renal Interest Society (IRIS). *IRIS Grading of AKI*; 2016. <http://www.iris-kidney.com/guidelines/grading.html>. Accessed June 19, 2022.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Brewer DJ, Macfarlane M, O'Connell E, Bacon NJ. Toxicity of zoledronic acid after intravenous administration: A retrospective study of 95 dogs. *J Vet Intern Med*. 2022;36(1):253-258. doi:10.1111/jvim.16335