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Evaluation of the Safety of Multiple Intramuscular Doses of Ketoprofen in Bearded Dragons (*Pogona vitticeps*)

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Abstract

Cyclooxygenase (COX) 1 has been shown to increase significantly in inflamed ophidian skin and chelonian muscles. Nonselective COX-1 and COX-2 inhibitors, such as ketoprofen, could therefore reduce inflammation more effectively than preferential COX-2 inhibitors in reptiles. The objective of this study was to evaluate potential adverse effects of ketoprofen in bearded dragons (*Pogona vitticeps*). Thirteen adult bearded dragons were divided into three groups receiving daily intramuscular injections for 14 days in a blinded randomized study design. Group 1 ($n = 5$) received saline, Group 2 ($n = 4$) received ketoprofen at 2 mg/kg (diluted 1:10 with saline) and Group 3 ($n = 4$) received ketoprofen at 20 mg/kg (undiluted). Biochemical values, fecal occult blood (FOB) tests, and blood clotting time were assessed before and after the 2-wk treatment. Renal, digestive, hepatic, and muscular histopathology was evaluated. Clinically, injection-site reactions were noted in Group 3 only ($n = 1/4$). No other clinical adverse effects were detected. No changes were detected in plasma biochemical values and clotting times before and after treatments, nor were changes detected between control and treatment groups. No lesion associated with ketoprofen toxicity was detected on histologic examination of the kidney, liver, and gastrointestinal tract. Lesions of muscular necrosis at the injection sites were of higher magnitude in Group 3 compared to Group 1. In conclusion, daily intramuscular administration of diluted ketoprofen at 2 mg/kg for 14 days did not cause adverse effects in a small number of bearded dragons, whereas severe muscular necrosis was detected at 20 mg/kg.

Key Words: Analgesia, antinociception, nonsteroidal anti-inflammatory drugs, pain management, *Pogona vitticeps*, reptile

Introduction

Bearded dragons (*Pogona vitticeps*) are common reptile companion animals frequently presented to veterinary clinics for medical conditions requiring the use of antinociceptive drugs. Among antinociceptive drugs used in veterinary medicine, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and alpha-adrenergic agonists are often prescribed (Duncan, 2012). Nonsteroidal anti-inflammatory drugs inhibit cyclo-oxygenase (COX) enzymes, which decreases the synthesis of prostanoids including prostaglandins, prostacyclins, and thromboxanes. Prostanoid inhibition provides desired peripheral antinociception, anti-inflammatory, and antipyretic effects. However, prostanoids have several physiological effects that are essentials for various normal metabolic functions. Consequently, NSAID administration can cause adverse effects in mammals such as a decrease in clotting functions, gastrointestinal ulcers, kidney, and liver damage (Budsberg, 2015).

There are two main isoforms of COX enzyme: COX-1 and COX-2. In mammals, preferential and selective COX-2 inhibitor NSAIDs are reported to produce fewer adverse effects than nonselective inhibitors, because COX-1 activity is preserved (Budsberg, 2015). However, this observation has not been documented in veterinary medicine, and selective COX-2 inhibitors can also produce adverse effects (Monteiro-Steagall *et al*., 2013). Depending on the species, COX-1 and COX-2 tissular expression varies, complicating extrapolation of adverse effects of NSAIDs from mammals

to reptiles (Grant, 2006). Two studies have evaluated COX-1 and COX-2 expression in reptiles. COX-1 significantly increased in inflamed muscles of box turtles (*Terrapene carolina carolina*) and in inflamed skin of ball pythons (*Python regius*) (Royal *et al*., 2012, Sadler *et al*., 2016). Therefore, nonselective COX inhibitors, such as ketoprofen, might be more effective in controlling inflammation in reptiles than preferential or selective COX-2 inhibitors.

Two pharmacokinetic studies of ketoprofen in reptiles (Tuttle *et al*., 2006; Thompson *et al*., 2018) have evaluated the dose of 2 mg/kg once daily. In green iguanas (*Iguana iguana*), a 2-mg/kg IV dose had a half-life of 31 h, which is longer than in mammals, and the bioavailability when administered IM was 78% (Tuttle *et al*., 2006). In loggerhead sea turtles (*Caretta caretta*), efficient plasma concentration in mammals was maintained for 12 to 24 h after administration of 2 mg/kg IV or IM in a multiple dose study (Thompson *et al*., 2018). In the same study, six turtles underwent a coelioscopy and received ketoprofen at 2 mg/kg IM once daily for 3 days. One individual developed anemia that resolved within 2 wk. The cause of anemia remained undetermined, but hypotheses included internal hemorrhage following coelioscopy or subcutaneous bleeding caused by repeated venipunctures (Thompson *et al*., 2018). In another study, eight loggerhead sea turtles received 2 mg/kg IM once daily for 5 days and no adverse effect was detected (Harms *et al*., 2021). To our knowledge, no ketoprofen pharmacodynamic study in reptiles have been published thus far. A high dose of ketoprofen (20 mg/kg) was administered to assess potential detrimental side effects of this medication at a higher dosage.

The objective of this study was to evaluate the safety of multiple intramuscular doses of ketoprofen in bearded dragons. The hypothesis was that daily intramuscular administration of ketoprofen at 2 mg/kg would not cause adverse effects while a dose of 20 mg/kg would cause renal, gastrointestinal, and hepatic lesions.

Materials and Methods

Animals and husbandry: This research project was approved by the Animal Care and Use Committee of the Université de Montréal (19-Rech-2051). Thirteen adult (>1 yr old) captive-bred wild-type bearded dragons were acquired, including eight females and five males. Weights ranged from 159 to 530 g. Bearded dragons were housed individually in glass terrariums (Exo Terra, Rolf C. Hagen Inc., Montreal, QC, Canada) in a temperature-controlled room at 28°C (82°F). Each terrarium was equipped with an ultraviolet-B-emitting lamp lit for 12 h/day, providing an optimal temperature gradient from 28°C (82°F) to 33°C (91°F) during the day. The photoperiod was set to provide 12 h of light and 12 h of darkness. Paper was used as substrate and a hiding box was provided.

Bearded dragons were fed three times per week with gut-loaded crickets (*Acheta domesticus*) and mealworms (*Tenebrio molitor*) dusted with calcium supplement (Exo Terra, Rolf C. Hagen). A mix of lettuce and carrots dusted with calcium supplement was provided daily and water was provided *ad libitum*. Each bearded dragon received goliath worms (*Manduca sexta*) and a 15-min bath weekly as enrichment.

During acclimation, complete physical examination, fecal occult blood (FOB) tests (Hemoccult II SENSA, Beckman Coulter, Brea, CA, USA), and fecal flotation tests in zinc sulfate were conducted. Because intestinal parasites (coccidia and pinworms) were detected in some individuals, all bearded dragons were treated with fenbendazole (Panacur, 100 mg/ml, Intervet Canada Corp., Kirkland, QC, Canada) and ponazuril (Marquis, 15% w/w, Merial Canada, Baie d'Urfé, QC, Canada), until fecal tests were negative for all individuals.

Study design: After a 3-wk acclimation period, the 13 bearded dragons were randomly divided into three groups. They received injections in alternating triceps muscles once daily for 14 d. Operators were blinded to treatment attribution: one operator prepared the drug each day with dragon identification numbers, and two distinct operators administered injections and assessed clinical signs. Group 1 ($n = 5$) received saline (sodium chloride, 0.9%, Baxter, Mississauga, ON, Canada), Group 2 ($n = 4$) received 2 mg/kg of ketoprofen (Anafen, 100 mg/ml, Merial Canada) (diluted 1:10 with saline; i.e., one part of ketoprofen solution and nine parts of saline), and Group 3 ($n = 4$) received 20 mg/kg of ketoprofen (undiluted). The 2-mg/kg dose was diluted to obtain the same volume as the 20-mg/kg dose and the volume of saline was identical (0.03–0.11 ml, or 0.2 ml/kg).

A blood sample was obtained from the ventral coccygeal vein of each individual prior to treatment and the day after the last treatment. Packed cell volume was assessed with capillary tubes (18,000 *g* for 3 min), total solids were measured by refractometry, whole blood clotting time evaluated with capillary tube method (nonheparinized microhematocrit capillary tubes, Fisherbrand, Pittsburgh, PA, USA), and a complete plasma biochemistry panel was obtained on heparinized blood. For clotting-time evaluation, capillary tubes were broken every 5 min up to 45 min and the first time point to visual clot detection was recorded, as reported elsewhere (Humble and Glover, 1950; Scanes, 2015). Values above 45 min were recorded as nonmeasurable. The biochemistry panel performed at the Faculté de médecine vétérinaire (Unicel DxC 600, Beckman Coulter) included alkaline phosphatase, aspartate transaminase, bile acids, total calcium, total cholesterol, creatine kinase (CK), glucose, lactate dehydrogenase, N-acetyl-beta-D-glucosaminidase, phosphorus, total proteins, urea, and uric acid. Calcium:phosphorus ratio was calculated. In addition, ionized calcium was obtained on a blood gas analyzer (Heska Element POC, Epocal Inc., Ottawa, ON, Canada). Changes in body weight were assessed twice weekly, and appetite, activity, abnormal clinical signs, and food intake were recorded daily. Fecal occult blood tests were performed a minimum of two times a week for each individual, starting on Day 2 and as soon as feces were available for testing afterwards. As recommended in product instructions (Hemoccult II SENSA,

Beckman Coulter), FOB tests were developed 3 days after stool sample application to allow degradation of fruit and vegetable peroxidases and avoid false-positive tests. Prey animals such as pinkie mice were not offered because meat can cause false-positive tests.

Postmortem examinations: After the 2-wk treatment, bearded dragons were sedated with 2 mg/kg morphine SC (Morphine Sulfate Injection USP, 10 mg/ml, Sandoz Canada, Boucherville, QC, Canada) and 5–15 mg/kg alfaxalone SC (Alfaxan Multidose, 10 mg/ml, Jurox Pty Ltée, Rutherford, NSW, Australia). Lizards were then euthanized with IV injections of 100 mg/kg pentobarbital sodium (Euthanyl, 340 mg/ml, Bimeda-MTC Animal Health, Cambridge, ON, Canada) and 2–4 mEq/kg potassium chloride (potassium chloride, 2 mEq/ml, Pfizer Canada, Kirkland, QC, Canada) followed by brain pithing. A complete necropsy was then performed. The entire gastrointestinal system was opened longitudinally and macroscopically examined to detect erosion and ulceration. Tissue samples were fixed in buffered formalin 10% including the heart, lung, liver, stomach, small intestine, colon, kidney, reproductive tract, and skin and muscle at the injection site. Formalin-fixed tissues were embedded in paraffin, sectioned at 5-µm thickness, and stained with hematoxylin, eosin, and safran after being mounted on glass slides. Histopathologic evaluation was blinded to treatment attribution. The presence of gastrointestinal erosions and ulcerations, and renal lesions were assessed for each individual. A semiquantitative grading system was established to grade vacuolization of hepatocytes, according to the percentage of hepatocytes cytoplasm occupied by lipidic vacuoles. Muscular histologic lesions at the injection sites were classified into three grades: Grade 1: mild and focal, Grade 2: moderate and multifocal, and Grade 3: marked and coalescing. Other pathological processes were noted on an individual basis.

Statistical analysis: Statistical analyses were performed using a statistical software (SAS v9.4, SAS Institute, Cary, NC, USA). The Kruskal-Wallis test was used to compare histological findings among groups and post hoc tests were then performed. Multiple comparisons were carried out between pairs of groups using a procedure previously described (Siegel and Castellan, 1998). Linear mixed models were used to compare blood parameters among groups, and before and after treatment, using the group, time, and their interaction as fixed factors and dragon identification as random factor. Normality of the residual values from each model was assessed graphically. For the linear models, pairs of means were compared using the sequential Benjamin-Hochberg procedure to adjust alpha values downward. The level of statistical significance was set at 0.05.

Results

During the 2-wk treatment period, no changes in appetite, activity, or body weight were observed. One individual from the 20-mg/kg treatment group presented stiff triceps muscles and blackish cutaneous lesions at the injection sites.

Five individuals displayed a positive FOB test result during the treatment period. Two out of five individuals of the control group had a positive test, including one diagnosed with a salpingitis and one with an egg yolk coelomitis. Three out of four individuals from the 20-mg/kg treatment group had positive FOB tests, including one diagnosed with an egg yolk coelomitis on necropsy. None of the individuals from the 2-mg/kg treatment group had positive FOB tests.

Plasma concentrations of six biochemistry parameters are presented in Figure 1. Packed cell volume, total solids, and plasma biochemical parameters were not significantly different before versus after treatment, nor were they significantly different between groups at any time points. Values were generally within normal limits for parameters with known reference intervals in bearded dragons (Ellman, 1997; Tamukai *et al*., 2011). In particular, uric acid concentration was lower in treated groups when comparing values before and after treatment, and it was lower in treated than in control groups at the end of experiment. Although nonsignificant, CK median value was higher posttreatment in the group receiving 20 mg/kg ketoprofen (see Fig. 1). Whole-blood clotting time assessed with capillary tubes was not significantly different before versus after treatment, nor was it different between groups. Clotting time could not be measured in 7 out of 26 tests because values above 45 min were recorded as nonmeasurable due to limited blood volume.

On macroscopic examination, a pale liver was noted in five individuals from the three groups. All individuals had some degree of hepatic lipidosis on histopathology, with lipids estimated to fill 20–90% of the cytoplasm of hepatocytes. However, the magnitude of the hepatic lipidosis was not statistically different between groups.

Two out of five individuals from the control group and one out of four individuals from the 2-mg/kg treatment group displayed mild (Grade 1) necrosis in the triceps muscles, while moderate (Grade 2) lesions of muscular necrosis were present in another individual from the 2-mg/kg treatment group. Histologically, Grade 1 and 2 muscular lesions were characterized by focal (respectively multifocal) muscular necrosis characterized by the presence of occasional fragmented and coagulated myocytes associated with mild focal to moderate multifocal fibrosis and hemorrhages in the interstitial spaces. All four individuals from the 20-mg/kg treatment group displayed Grade 3 lesions. These lesions were associated with large areas of muscular necrosis composed of swollen and hyperacidophilic fragmented and coagulated myocytes associated with an extensive fibrosis of the interstitial spaces with infiltration of numerous heterophils and macrophages (Fig. 2). The magnitude of the lesions was statistically different among groups ($P = 0.013$) with higher grades in Group 3 than in Group 1. No gastrointestinal ulcers or erosions were noted at gross necropsy or at histopathologic

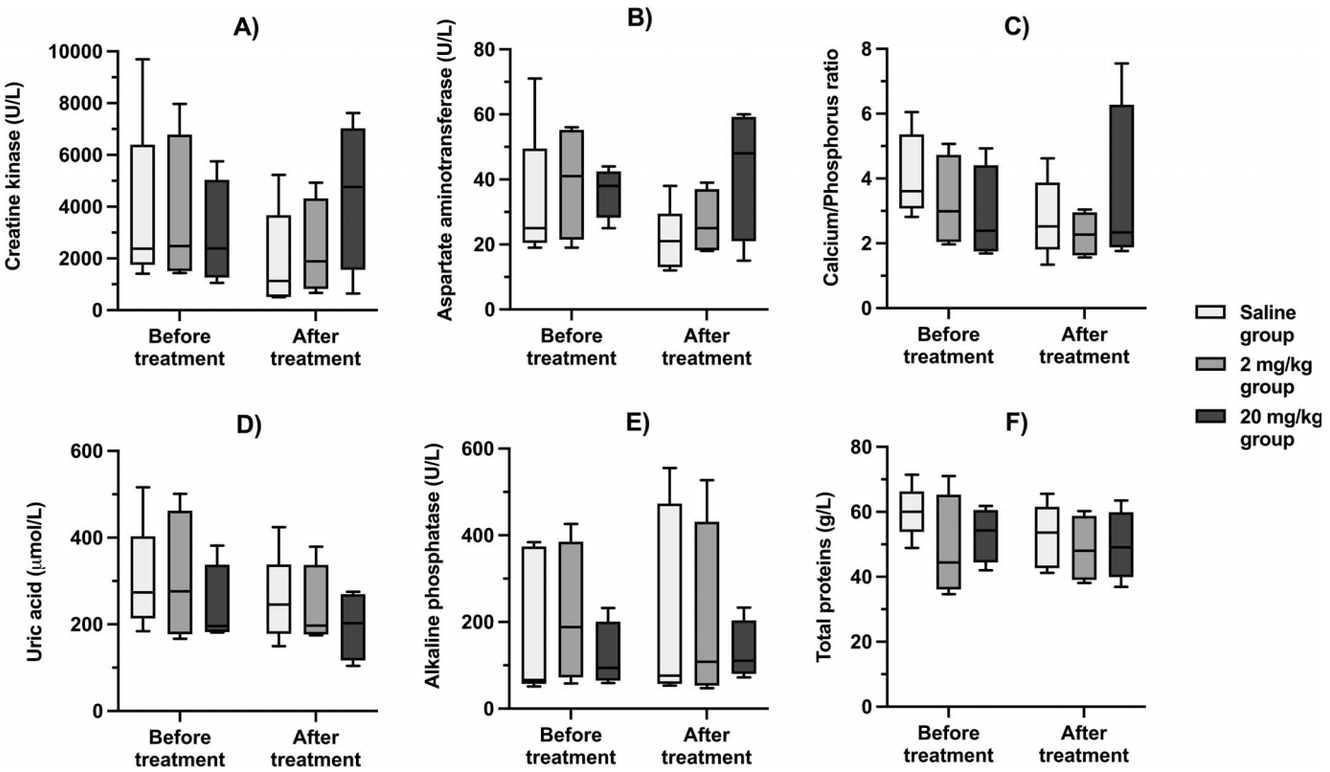

Figure 1. Plasma concentrations of six biochemistry parameters before and after administration of saline ($n = 5$), 2 mg/kg ($n = 4$), or 20 mg/kg ($n = 4$) of ketoprofen once daily for 14 days in 13 bearded dragons (*Pogona vitticeps*): (A) Creatine kinase (CK), (B) aspartate aminotransferase (AST), (C) calcium/phosphorus ratio, (D) uric acid, (E) alkaline phosphatase (ALP), (F) total proteins.

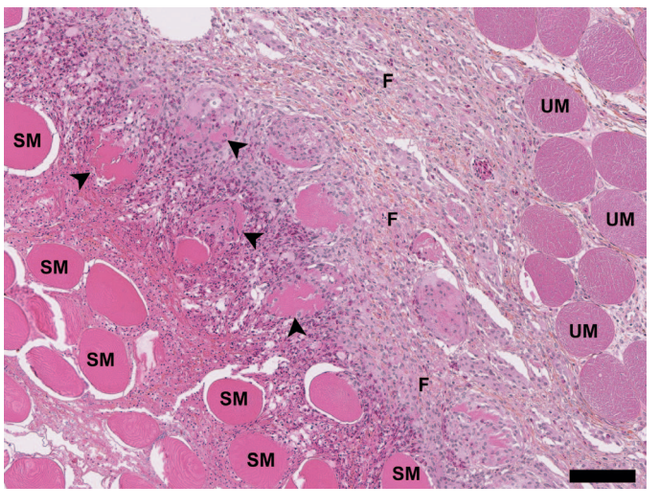

Figure 2. Photomicrograph of intramuscular injection site from a bearded dragon (*Pogona vitticeps*) treated with 20 mg/kg of ketoprofen once daily for 14 days, showing an area of extensive muscular necrosis characterized by the presence of swollen hyperacidophilic myocytes (SM), fragmented and coagulated myocytes (arrowheads) and marked fibrosis of the interstitial space (F) infiltrated by numerous heterophils and macrophages. Unaffected myocytes are also present on this section (UM) (bar = 100 μm, hematoxylin, eosin and safran stain).

examination in any individual. No renal lesion suggestive of an acute toxic effect was detected. Chronic mild renal lesions were noted in all three groups, including mesangial thickening, glomerulosclerosis, interstitial fibrosis, and cytoplasmic brown pigments in the proximal tubules.

Discussion

Based on the parameters evaluated in the present study, the administration of ketoprofen at 2 mg/kg IM diluted 1:10 in saline once daily for 14 days appeared to be safe in healthy adult bearded dragons. Conversely, a dose of 20 mg/kg IM q24h for 14 days caused adverse effects.

A 2-wk treatment duration was chosen because metabolism and healing time is slower in reptiles than in mammals, so lizards could presumably benefit from a longer administration of anti-inflammatory drugs (Duncan, 2012). For example, wounds sutured after surgery typically heal within 2 wk in mammals compared to 4–8 wk in reptiles (Mader *et al.*, 2006). However, there is currently little evidence to support the dosage, frequency, duration, and route of administration of NSAIDs in reptiles (Trnkova *et al.*, 2007; Divers *et al.*, 2010; Lai *et al.*, 2015; Uney *et al.*, 2016).

Only few studies have evaluated adverse effects of NSAIDs in reptiles, including one that evaluated ketoprofen safety in loggerhead sea turtles. In this study, eight

individuals received 2 mg/kg IM once daily for 5 days, and eight control individuals received saline (Harms *et al*., 2021). No adverse effects were noted on body weight, clinical appearance, hemostasis assessed with thromboelastography, hematology, and plasma biochemistry parameters. There was no statistically significant difference between treatment groups, or before and after treatments. However, necropsies were not conducted in this study and the sensitivity of biochemistry parameters to detect organ lesions may be suboptimal in reptiles (Wilkinson and Divers, 2020). In four green iguanas, daily oral administration of meloxicam at high doses (1 or 5 mg/kg) for 12 days did not cause histological changes in gastric, hepatic, or renal tissues (Divers *et al*., 2010). In another study on green iguanas, seven individuals received a daily intramuscular injection for 10 days of carprofen (2 mg/kg) and five individuals received meloxicam (0.2 mg/kg). No changes of clinical importance in hematological and biochemical parameters were noted, and values were within reference limits (Trnkova *et al*., 2007).

In the present study, the only adverse effect of ketoprofen was the induction of muscular necrosis at the injection sites. Histologically, extensive lesions of muscular necrosis were observed at the injection sites in all individuals of the 20-mg/kg group. Clinically, one individual also displayed stiff triceps muscles and blackish cutaneous coloration suggestive of tissue necrosis. No significant difference in plasma CK concentration was noted among groups, despite significantly different grades of muscular necrosis. This might be because of the low number of individuals included in the study. The mild muscular necrosis observed in the saline and 2-mg/kg groups were presumably associated with the mechanical trauma associated with the insertion of the needle. The marked difference in muscle necrosis observed between the 2 mg/kg and the 20-mg/kg groups might be a consequence of the actual dose of ketoprofen used or because ketoprofen was injected undiluted in the 20-mg/kg group. Even if our study cannot discriminate between these two hypotheses, our results suggest that ketoprofen should be diluted for IM administration regardless of the dose administered pending additional studies addressing this. The Anafen® product label states that ketoprofen pH is adjusted with citric acid, but pH value is not mentioned. Therefore, it remains uncertain whether pH could be responsible for the observed muscular lesions. In birds, intramuscular administration of ketoprofen does not induce muscular lesions (Machin *et al*., 2001), contrary to carprofen, flunixin meglumine, and meloxicam that caused myositis and muscular necrosis (Machin *et al*., 2001; Zollinger *et al*., 2011; Sinclair *et al*., 2012). A study evaluating injection-site tolerance of Ketofen® (ketoprofen, 100 mg/ml, Zoetis Inc., Kalamazoo, MI, USA) showed that SC injections of ketoprofen in cattle induced macroscopic tissue discoloration and histological changes including fibrosis, hemorrhage, fibrin accumulation, necrosis of adipose tissue, and mixed cell inflammation (Food and Drug Administration, 2021). These findings are similar to those noted in the present study. The small size of the triceps muscles of bearded dragons probably contributed to the severity of muscular lesions. Indeed, multiple intramuscular injections into a small muscle mass can cause myositis, myopathies, paresis, and ambulatory difficulties (Perry and Mitchell, 2019). Hydration status and body temperature should be adequate to ensure appropriate muscular perfusion prior to IM injections (Perry and Mitchell, 2019). In addition, SC administration should be favored whenever supported by evidence-based studies.

No toxic effects on the gastrointestinal system were detected on postmortem examination. Two individuals had an egg yolk coelomitis and one individual had a salpingitis, which could have caused bleeding into the cloaca and thus positive FOB tests (Stahl and DeNardo, 2019). Bearded dragon reproductive, urinary, and digestive tracts empty into the cloaca. Thus stools can be contaminated with blood from these systems, causing a positive FOB test (Gibbons *et al*., 2006). Two individuals from the 20-mg/kg treatment group had a positive FOB test without lesions noted in their reproductive or urinary systems. Alternatively, the hemoglobin contained in a red meat diet is known to cause false-positive FOB tests. The composition of insects' hemolymph differs from mammalian blood, and it is unknown if the insect-based diet of bearded dragons could have altered the results of the tests. In brief, it is not possible to conclude if these positive tests are suggestive of gastrointestinal bleeding because of concomitant morbidities and lack of validation of this test in reptiles. Although regularly reported in mammals, gastrointestinal lesions associated with NSAID administration have only rarely been reported in birds. In American kestrels (*Falco sparverius*), administration of high dosages of oral meloxicam caused gross punctiform erosions of the proventriculus/ventriculus, and histopathological evaluation showed mucosal ulceration and mineralization of the gastric mucosa (Summa *et al*., 2017).

No toxic effect of ketoprofen on the kidney was detected via biochemistry or histopathology. Histologically, no acute tubular degeneration or necrosis was noted, which is a common renal lesion associated with NSAID toxicity (Breshears and Confer, 2017). Compared with mammalian kidneys, which have millions of nephrons, reptile kidneys contain only thousands of nephrons, which could hypothetically be more susceptible to renal toxicity (Rockwell and Mitchell, 2019). Chronic renal histological changes were observed in all three groups and were considered unrelated to treatment. Chronic glomerulonephritis in reptiles is characterized by fibrosis, glomerular tuft sclerosis, and tubular nephrosis (Origgi, 2018). Deposition of brown pigments in tubular epithelial cells is another common finding and is described as melanin degradation product (Origgi, 2018). Susceptibility to renal toxicity associated with NSAIDs administration differs between avian species and extrapolation from one species to another should be done with caution (Rattner *et al*., 2008). Old World *Gyps* vultures are extremely susceptible to NSAID toxicity, with adverse effects including acute tubular

necrosis, visceral gout, and renal insufficiency, which often lead to death (Swan *et al*., 2006). On the other hand, kestrels do not display renal lesions when administered high doses of meloxicam up to 20 mg/kg (Summa *et al*., 2017).

No toxic effect of ketoprofen on the liver was detected via biochemistry or histopathology. Hepatic lipidosis severity was not significantly different among groups, which suggests that this finding was not related to the treatment. Fat deposition in hepatocytes is a common finding in captive reptiles (Origgi, 2018; Divers, 2019). It can reflect a physiological or pathological process and can be influenced by several factors including species, age, gender, reproductive, and nutritional status. High-fat diet and lack of exercise are common causes of hepatic lipidosis. Studies in birds have reported liver toxicity, characterized by hepatic lipidosis and necrosis, associated with administration of various NSAIDs such as carprofen, diclofenac, and meloxicam (Hussain *et al*., 2008; Zollinger *et al*., 2011; Summa *et al*., 2017).

No difference in blood clotting time was detected among groups before and after treatment, but evaluating clotting function with the capillary tube method has a low sensitivity (Bigland and Starr, 1965). Other techniques, such as platelet function analysis, could be used in future studies, as viscoelastic techniques are poor indicators of platelet function (Whiting *et al*., 2015). These techniques would need to be validated in reptiles first. In mammals, NSAIDs can increase blood clotting time by inhibiting COX-1 enzyme in platelets, which inhibits thromboxane A_2. Mammalian platelets lack a nucleus to synthetize proteins, which causes a prolonged antithrombotic effect. It is hypothesized that NSAIDs could have less effect on blood clotting time in reptiles because they have nucleated thrombocytes that could produce new enzymes (Dijkstra *et al*., 2015). However, little is known about reptile coagulation and no gold-standard technique has been described in bearded dragons to date.

Additional limitations of the study include the small number of individuals used. Although bearded dragons were considered healthy based on physical examination, blood tests, and FOB tests, two individuals were affected by an egg yolk coelomitis. Moreover, the capillary tube method and FOB tests have not been validated in reptiles yet; thus results must be interpreted with caution.

Research perspectives following this project include the comparison of effects of meloxicam and ketoprofen and a pharmacodynamic study of ketoprofen in reptiles. Future studies could also evaluate the effects of oral and subcutaneous administration of ketoprofen, as it could potentially be less irritating than intramuscular injections.

In conclusion, administration of ketoprofen at 2 mg/kg IM diluted 1:10 with saline once daily for 14 days did not cause adverse effects in this limited number of bearded dragons. The absence of renal and hepatic adverse effects with 20 mg/kg IM once daily for 14 days suggests a wide therapeutic margin for ketoprofen in bearded dragons. However, the occurrence of severe muscular necrosis with this dosage suggests that the repetitive use of high-dose undiluted ketoprofen can be irritating for the muscular tissues. The results of this study will improve reptile antinociceptive management by allowing the use of a nonspecific COX inhibitor and highlighting which adverse effects should be monitored when this medication is administered. However, it is worth remembering that antinociception properties of ketoprofen remain to be studied in reptiles. The same precautions as recommended in mammals should be implemented when administering NSAIDs to reptiles, including proper hydration, appetite and injection site monitoring, as well as adjustment of the dosage based on the renal and hepatic health of the animal.

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