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Pharmacokinetic Profiles of Meloxicam and Sustained-release Buprenorphine in Prairie Dogs (*Cynomys ludovicianus*)

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In this study, we evaluated the pharmacokinetic profiles of meloxicam and sustained-release (SR) buprenorphine in prairie dogs. The 4 treatment groups were: low-dose meloxicam (0.2 mg/kg SC), high-dose meloxicam (4 mg/kg SC), low-dose buprenorphine SR (0.9 mg/kg SC), and high-dose buprenorphine SR (1.2 mg/kg SC). The highest plasma concentrations occurred within 4 h of administration for both meloxicam treatment groups. The therapeutic range of meloxicam in prairie dogs is currently unknown. However, as compared with the therapeutic range documented in other species (0.39 – 0.91 μg/mL), the mean plasma concentration of meloxicam fell below the minimal therapeutic range prior to 24 h in the low-dose group but remained above therapeutic levels for more than 72 h in the high-dose group. These findings suggest that the current meloxicam dosing guidelines may be subtherapeutic for prairie dogs. The highest mean plasma concentration for buprenorphine SR occurred at the 24-h time point (0.0098 μg/mL) in the low-dose group and at the 8-h time point (0.015 μg/mL) for the high-dose group. Both dosages of buprenorphine SR maintained likely plasma therapeutic levels (0.001 μg/mL, based on previous rodent studies) beyond 72 h. Given the small scale of the study and sample size, statistical analysis was not performed. The only adverse reactions in this study were mild erythematous reactions at injection sites for buprenorphine SR.

Abbreviations: SR, sustained release; COX, cyclooxygenase

Pain assessment and management is an essential component of effective medical treatment that requires continual reevaluation throughout the case to ensure that changing needs are addressed appropriately. Selection of an optimal analgesic depends on many factors, including age, species, administration, and classification of pain, thus potentially increasing complexity in the decision-making process. Ideally, in a research environment, analgesic choice would address the clinical needs of the animal yet minimize the potential for side effects and interference with research.

Pain is a complex sensation that all vertebrates experience in response to actual or potential tissue damage; common pain classifications include acute, chronic, cancer, and neuropathic.[16] Analgesia is defined as lack of pain without loss of consciousness, in which the goal of drug intervention is to achieve a balanced state during which an animal is neither substantially hindered by pain nor adversely affected by the side effects of the drugs.[20] Multimodal analgesia maximizes the beneficial analgesic effects of multiple drugs through synergistic interactions in an effort to minimize adverse drug effects by lowering the dose of any individual drug.[16] Pain control is also improved through working on different targets of the pain pathway. The multimodal effect can be achieved by 3 techniques: (1) combining drugs with different pharmacologic mechanisms, (2) using different routes of administration for drugs with similar modes of action, and (3) using drugs that may counteract the potential side effects of each drug.[4]

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NSAID are one category of drug commonly used to address pain in veterinary medicine, and they are considered to be effective against pain of low to moderate intensity.[10] NSAID inhibit the enzyme cyclooxygenase (COX) and can be selective or nonselective inhibitors of the COX1 and COX2 enzymes. COX1 resides in tissues of the body and catalyzes the formation of prostaglandins which mediate a variety of normal physiologic effects. In contrast, COX2 is activated in damaged and inflamed tissues and catalyzes the formation of prostaglandins that are associated with intensifying the inflammatory response. In general, the analgesic action of analgesic–antipyretic and antiinflammatory drugs is due to COX2 inhibition, and the side effects are due to COX1 inhibition. Most NSAID are metabolized in the liver and excreted by the kidneys or bile.[17] The side effects of NSAID are dose-dependent and commonly include gastrointestinal toxicity, coagulopathy, and renal and hepatic failure.[21] Meloxicam is considered a selective COX2 NSAID in rodents and is effective for both inflammatory and neurogenic pain.[7] In prairie dogs, suggested dosage for meloxicam is 0.1 to 0.2 mg/kg SC or PO every 24 h.[23]

Opioids are another drug class and mimic the effects of endogenous opioids through μ, δ, and κ receptors. In general, opioids are employed against acute, chronic, and cancer pain.[10] Buprenorphine is a synthetic partial μ receptor agonist and is a preferred analgesic to relieve moderate postsurgical pain in rodents.[7] Buprenorphine is metabolized by the liver and excreted in the bile, with reported side effects including decreased weight gain, pica, respiratory depression, and decreased water consumption.[3,25] In prairie dogs, the recommended dosage for buprenorphine is 0.01 to 0.05 mg/kg SC or IP every 6 to 12 h.[23]

Currently, a veterinary compounding pharmacy is marketing a formulation of buprenorphine in a sustained-release

biodegradable polymer delivery system which has demonstrated analgesic efficacy over a 72-h time period in rats.[5] Reduced frequency of dosing would be a dramatic refinement in the management of prairie dogs, because it would decrease occupational risk as well as stress associated with handling, restraint, and readministration of drugs in the animals.[3] Using a formulation that can address pain over an extended duration would be extremely beneficial in environments and facilities that do not provide 24-h onsite staffing.

At the Centers for Disease Control and Prevention, prairie dogs are used as a model for monkeypox virus research. Since the eradication of smallpox, monkeypox has become the most significant public health threat within the genus *Orthopoxvirus*, because it is a known zoonosis.[11] We aim to enhance the pain management of the prairie dogs within our colony with a focus on commonly used and available analgesics. The purpose of this study is to evaluate the pharmacokinetic profiles of meloxicam and buprenorphine SR in a population of black-tailed prairie dogs (*Cynomys ludovicianus*). To date, no research has been published on the pharmacokinetic profiles in this species, and we hope to contribute to improvement of analgesic therapy in these animals. Our hypothesis is that buprenorphine SR will achieve the proposed therapeutic plasma concentration of 0.001 µg/mL for 72 h that is effective in other species.[5] We also hypothesize that meloxicam will maintain plasma levels in the therapeutic range noted in other species (0.39–0.91 µg/mL) for 24 h.[9,13]

Materials and Methods

Animal care and use program. All animals were handled in strict accordance with the *Guide for the Care and Use of Laboratory Animals*.[12] All animal work was approved by the Centers for Disease Control IACUC and was performed in an AAALAC-accredited facility.

Animals. Wild-caught juvenile black-tailed prairie dogs (*Cynomys ludovicianus*) were obtained from Texas through a vendor that used humane live-trapping techniques. The animals were transported to the Centers for Disease Control and Prevention (Atlanta, GA) for infectious disease research, where they were quarantined for 30 d, microchipped, and housed until use. When not on study, the prairie dogs were maintained as a floor-housed mixed-sex colony, with 20 to 30 animals per group and crinkle-paper bedding for burrowing purposes. Animals were given a commercial prairie dog diet (Brisky Pet Products, Franklinville, NY) and water without restriction, with enrichment consisting of peanuts, apples, carrots, sweet potatoes, and sunflower seeds. For our study, 16 adult (8 male, 8 female) 7-y-old age-matched prairie dogs were selected on the basis of weighing a minimum of 800 g (range, 810 to 1190 g) to minimize possible adverse reactions from multiple blood draws. Animals were allowed to acclimate to single housing for 3 d prior to the start of study. Single housing was provided within IVC containing crinkle-paper bedding and a cardboard tube for enrichment. Single housing was used to facilitate monitoring of individual animals for adverse events such as inappetence and diarrhea.

Drug administration and blood collection. Meloxicam (5 mg/mL; Metacam, Boehringer-Ingelheim, Ridgeland, CT) and buprenorphine SR (1 mg/mL; Zoopharm, Fort Collins, CO) were used in this study. The 16 prairie dogs were divided into 4 groups (each containing 2 males and 2 females): low-dose meloxicam (0.2 mg/kg), high-dose meloxicam (4 mg/kg), low-dose buprenorphine SR (0.9 mg/kg), and high-dose buprenorphine SR (1.2 mg/kg). The dosages selected for meloxicam and buprenorphine SR were from previous rodent studies.[5,7,23]

For all manipulations, the prairie dogs were anesthetized with 5% isoflurane and maintained on 1% to 3% isoflurane. Baseline blood samples (0.7 mL) were collected intravenously from the medial saphenous or cranial vena cava at time point 0, and drugs were administered subcutaneously between the shoulder blades immediately after baseline collection. The same volume and technique for blood collection was performed at 4, 8, 24, 48, 72 and 96 h after drug administration. The blood was put in EDTA tubes, centrifuged at 268 × *g* for 15 min; plasma was removed, aliquoted into cryotubes, and stored at –80 °C until sample analysis. The animals were monitored twice daily by research and animal care staff, and no adverse reactions to the multiple anesthetic episodes occurred.

Measurement of plasma meloxicam concentrations. The plasma samples were analyzed by HPLC. The HPLC system consisted of a quaternary solvent-delivery system (flow rate, 1 mL/min), an autosampler (1200 series, Agilent Technologies, Wilmington, DE), and a UV detector (1200 series Variable Wavelength Detector, Agilent Technologies) set at a wavelength of 279 nm. Chromatograms were integrated by using a computer program (OpenLAB software, Agilent Technologies). The column was a reverse-phase, C18 column (4.6 mm × 15 cm; Zorbax Rx-C18, MAC-MOD Analytical, Chadds Ford, PA) kept at a constant temperature of 40 °C. The mobile phase for HPLC analysis consisted of 40% acetonitrile, 60% 0.05 M sodium acetate. Glacial acetic acid was added to the buffer to adjust the pH to 3.7 to 3.8. Fresh mobile phase was prepared, filtered (0.45 µm), and degassed for each day's run. The assay method was similar to previous studies but validated specifically for this study by fortifying blank (control) prairie dog plasma from untreated animals.[2,24]

The reference standard of meloxicam (USP, Rockville, MD) was used to prepare a stock solution that was used to fortify the blank sample matrix. The meloxicam calibration curve consisted of 8 standard solutions that ranged between 0.01 and 10 µg/mL and included a blank (0 µg/mL) sample. The blank sample was used to detect interfering peaks that elute into the window of the chromatographic peak of interest and to measure background interference. The calibration curve was accepted when the linear coefficient of determination (R^2) was 0.99 or greater and when the calibration curve concentrations could be back-calculated to within 15% of the true concentration of the standard. Fresh calibration curves were prepared for each day's analysis. The retention time for the peak of interest was approximately 4.9 to 5.0 min. Limit of quantification for meloxicam in prairie dog plasma in the samples was 0.01 µg/mL, which was determined from the lowest point on a linear calibration curve that yielded acceptable accuracy and within accepted guidelines for the signal-to-noise ratio.

Measurement of plasma buprenorphine SR concentrations. Prairie dog plasma samples were analyzed by UPLC followed by detection with tandem mass spectrometry, using blank prairie dog plasma for validation. Calibration curves and quality controls were prepared by fortifying blank plasma with stock solutions of buprenorphine hydrochloride (Sigma-Aldrich, St. Louis, MO) dissolved in 100% methanol. Plasma samples, standards, and quality controls were then prepared by adding 100 µL to 400 µL methanol in a glass tube and vortexing for 20 s. The sample mixture was centrifuged at 1500 × *g* for 10 min, and the supernatant was removed, placed in an evaporator, and dried under a stream of nitrogen (20 psi) for 40 min at 40 °C. Samples were reconstituted in 250 µL 50:50 acetonitrile:water (v/v) containing 0.1% formic acid. Volumes of 4 µL for samples and standards were injected into the UPLC system (Acquity

Classic UPLC with Acquity I Class UPLC with an Acquity Xevo TQD mass spectrometer, Waters Corporation, Milford, MA) at a flow rate of 0.3 mL/min. A gradient was used, and the initial mobile phase was 0.1% formic acid in water:0.1% formic acid in acetonitrile (85:15, v/v) for the first 2.5 min. The mobile phase then was switched to 10:90 (v/v) for 2.5 to 4 min. During the last 1 min of the run, the mobile phase was 85:15 (v/v). The Xevo TQD was run in the ESI+ mode. The quantification multiple-reaction monitoring transition was 468.39 → 100.89. Column temperature was maintained at 40 °C and sample temperature was maintained at 10 °C. Separation was achieved by using an Acquity UPLC HSS T3 column (1.8 µm, 2.1 × 100 mm) and Vanguard column (Waters Corporation). The retention time observed for buprenorphine was 1.49 min. Standard curves were linear over a concentration range of 0.1 to 20 ng/mL, with an R2 ≥ 0.99 daily. The lower limit of quantification was 0.1 ng/mL, which was determined from the lowest point on a linear calibration curve that met our acceptance criteria and by using guidelines published by the United States Pharmacopeia.[22] The accuracy (mean ± 1 SD) of the assay was 95.1% ± 3.3%, and the average precision (relative standard deviation) was 5.6% ± 0.8%.

Pharmacokinetic analysis. Noncompartmental analysis of the data was performed by using commercially available software (Phoenix WinNonLin, version 6.3, Certara, St Louis, MO). The area under the concentration–time curve was determined by using the trapezoidal rule, with a linear up, log down method. Standard noncompartmental equations were used.[6,8] Values for peak plasma concentration and the time at peak concentration were taken directly from the data. Given the small scale of the study and sample size, statistical analysis was not performed.

Results

Pharmacokinetics. The plasma concentrations of meloxicam (Figure 1) and buprenorphine SR (Figure 2) were calculated over a 96-h period.

Meloxicam. Reported therapeutic levels vary widely for other species (0.39–0.91 µg/mL) except for rodents.[9,13] Other papers have used this range as a guide for their studies as more research needs to be done in this area.[14] For both meloxicam groups, the mean plasma concentration levels reached proposed therapeutic levels between 0 and 4 h. The highest mean plasma concentrations in the low- and high-dose groups were seen at the 4-h time point and were 1.09 and 23.33 µg/mL, respectively. Plasma concentrations in the low-dose group stayed above proposed therapeutic levels for at least 8 h but were below proposed therapeutic levels at the 24-h time point. Plasma concentrations in the high-dose group stayed above proposed therapeutic levels for at least 72 h but were below proposed therapeutic levels at the 96-h time point. The mean half-life for meloxicam was 13.84 ± 1.68 h in the low-dose group and 14.42 ± 2.93 h in the high-dose group (Tables 1 and 2).

Buprenorphine. The proposed therapeutic plasma concentration level for buprenorphine SR is 0.001 µg/mL.[5] This level has been used in research in other species, because this formulation has only recently been developed, and more research needs to be performed.[14] For both buprenorphine SR groups, the mean plasma concentrations levels reached proposed therapeutic levels between 0 and 4 h after administration. The highest mean plasma concentration occurred at the 24-h time point in the low-dose group and at the 8-h time point in the high-dose group and were 0.010 µg/mL and 0.015 µg/mL, respectively. In both groups, these concentrations stayed above proposed therapeutic levels, with the mean plasma concentration at 0.003 µg/mL for the low-dose group and at 0.002 µg/mL for the high-dose group. The average half-life for buprenorphine SR was 39.15 ± 18.44 h in the low-dose group and 19.53 ± 1.12 h in the high-dose group (Tables 3 and 4).

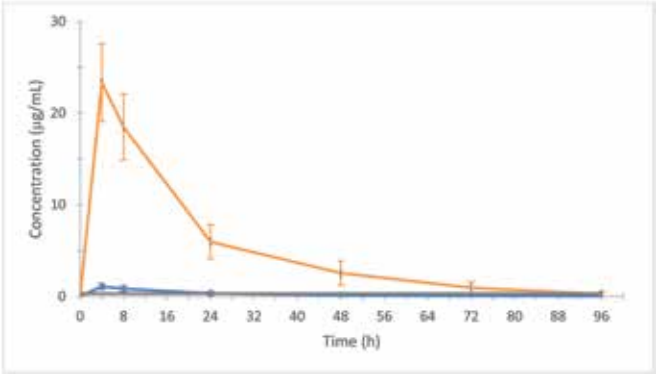

Figure 1. Plasma concentration of meloxicam in prairie dogs at 0, 4, 8, 24, 48, and 72 h after a single injection of 0.2 mg/kg SC (blue) or 4 mg/kg SC (orange); gray line indicates target therapeutic level.

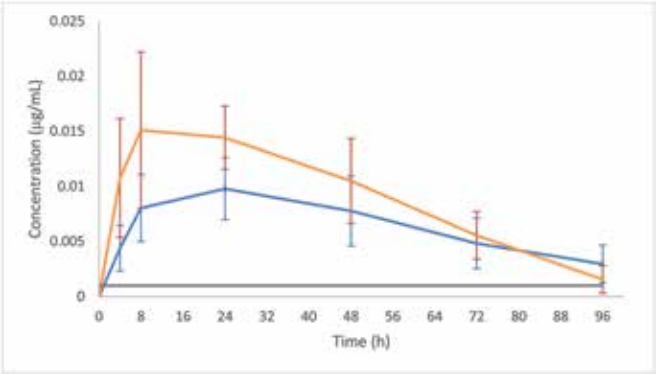

Figure 2. Plasma concentration of buprenorphine SR in prairie dogs at 0, 4, 8, 24, 48, and 72 h after a single injection of 0.9 mg/kg SC (blue) or 1.2 mg/kg SC (orange); gray line indicates target therapeutic level.

Adverse effects. Adverse effects developed in 4 animals across both buprenorphine-treated groups, with injection site reactions appearing within 2 to 4 d after the injections were given Figure 3). The reactions were seen in both treatment groups and included erythema and scabbing at the site of injection. The wounds were clipped and cleaned (Nolvasan, Zoetis) and completely healed within 2 wk without further intervention. No adverse effects were seen in the meloxicam-treated animals. The prairie dogs had no other clinical concerns during the study.

Discussion

The present study assessed 2 analgesics for pain management in prairie dogs. According to our data, the low dose of meloxicam did not maintain proposed therapeutic levels as reported in other species for 24 h, whereas the high dose maintained the maximal proposed therapeutic level (0.91 µg/mL) past the 72-h time point. We chose 0.2 mg/kg as the low dose for meloxicam because it is commonly used in prairie dogs, although 1 to 2 mg/kg is used in other rodents.[18,23] The results of this study suggest that the dose of 0.2 mg/kg may not achieve appropriate therapeutic concentration levels with a 24-h dosage regimen. In comparison, the high dose of 4 mg/kg was chosen in light of the dose range (1–4 mg/kg) used in rodents.[7] Our results suggest that the high dose of 4 mg/kg would maintain therapeutic levels for 72 h without redosing. Future research

Table 1. Noncompartmental analysis of meloxicam at 0.2 mg/kg SC

	Prairie dog					
	1	2	3	4	Mean	1 SD
Area under the time–concentration curve, h × µg/mL	21.799	14.386	39.681	21.794	24.415	10.760
Area under the first moment curve, h × h × µg/mL	367.629	283.613	901.185	448.475	500.226	275.650
Clearance, mL/h/kg	9.175	13.903	5.040	9.177	9.324	3.622
Maximal serum concentration, µg/mL	1.293	0.730	1.747	1.059	1.207	0.428
Half-life, h	11.690	13.665	15.742	14.263	13.840	1.678
Mean resident time, h	16.865	19.715	22.711	20.578	19.967	2.421
Volume of distribution, mL/kg	154.731	274.093	114.467	188.833	183.031	67.891

Table 2. Noncompartmental analysis of meloxicam at 4 mg/kg SC

	Prairie dog					
	5	6	7	8	Mean	1 SD
Area under the time–concentration curve, h × µg/mL	375.416	663.518	481.743	622.994	535.918	132.363
Area under the first moment curve, h × h × µg/mL	7297.373	17870.926	8323.225	12183.779	11418.826	4788.315
Clearance, mL/h/kg	10.655	6.028	8.303	6.421	7.852	2.116
Maximal serum concentration, µg/mL	19.313	24.635	27.883	31.856	25.922	5.304
Half-life, h	13.473	18.669	11.976	13.556	14.418	2.925
Mean resident time, h	19.438	26.934	17.277	19.557	20.801	4.220
Volume of distribution, mL/kg	207.110	162.368	143.456	125.567	159.625	35.041

Table 3. Noncompartmental analysis of buprenorphine at 0.9 mg/kg SC

	Prairie dog					
	9	10	11	12	Mean	1 SD
Area under the time–concentration curve, h × µg/mL	0.361	0.539	0.747	0.849	0.624	0.218
Area under the first moment curve, h × h × µg/mL	12.760	24.512	31.152	36.732	26.289	10.310
Clearance, mL/h/kg	2376.000	1010.000	1004.000	830.000	1305.000	718.863
Maximal serum concentration, µg/mL	0.008	0.730	0.012	0.013	0.191	0.360
Half-life, h	19.800	64.200	37.300	35.300	39.150	18.441
Mean resident time, h	35.400	45.500	41.700	43.300	41.475	4.339
Volume of distribution, mL/kg	67.747	93.640	54.065	42.255	64.427	22.086

Table 4. Noncompartmental analysis of buprenorphine at 1.2 mg/kg SC

	Prairie dog					
	13	14	15	16	Mean	1 SD
Area under the time–concentration curve, h × µg/mL	0.850	1.085	0.882	0.634	0.863	0.185
Area under the first moment curve, h × h × µg/mL	26.788	46.003	28.174	25.548	31.628	9.643
Clearance, mL/h/kg	1369.000	1009.000	1312.000	1842.000	1383.000	344.381
Maximal serum concentration, µg/mL	0.023	0.016	0.019	0.011	0.017	0.005
Half-life, h	18.900	21.200	19.100	18.900	19.525	1.121
Mean resident time, h	31.500	42.400	31.900	40.300	36.525	5.639
Volume of distribution, mL/kg	37.361	30.940	36.108	50.248	38.664	8.207

should investigate the administration of meloxicam at 1 to 2 mg/kg given that the current recommended dosage appears subtherapeutic in this species.

The buprenorphine SR data shows that both doses, which were chosen based on previous studies in other rodents, maintained plasma levels above the suggested therapeutic level (0.001 µg/mL) beyond the 96-h time point.[5] As a result, dosage of buprenorphine SR at 0.9 mg/kg every 96 h would be the revised proposed current recommendation for prairie dogs, because we strive to use the minimal amount of drug that achieves our treatment goals.

The injection site reactions seen in a subset of the prairie dogs in this study highlight concerns regarding the use of buprenorphine SR in animals. Similar lesions have been reported in other species, including mice and NHP.[14,19] Importantly, differentiating between drug-associated adverse events and the effects of experimental inoculations with various infectious agents, such as monkeypox virus, that cause similar lesions may be difficult. Slowly withdrawing the needle after injection and pinching the injection site for 15 s has been reported to reduce the incidence of lesion development.[5]

Figure 3. Prairie dog with injection site reaction, showing erythema and edema at 48 h after injection of buprenorphine SR.

We recognize several limitations in the current study that reduce the generalizability of the results. The small sample size ($n = 4$ animals per group) was due to the availability of animals currently in the colony. Previous pharmacokinetic studies had the same sample size.[11] Interindividual variation is an important consideration, because a single outlier can severely skew data results when sample sizes are relatively small. As an example in the current study, one animal in the low-dose meloxicam group had no drug detected at the 96-h time point. In addition, the drug half-lives varied markedly among the animals in the low-dose buprenorphine SR group, perhaps reflecting the small sample size or interindividual variation. In light of these limitations, statistical analysis was not performed. Furthermore, age- and sex-associated differences can affect the pharmacokinetic action of drugs.[15] Sex-associated differences exist in metabolism of meloxicam in humans and rats,[1] and examining this effect in prairie dogs would be prudent.

Another limitation to this study involved the time points of blood collection, which were based on other pharmacokinetic studies.[5] Although the highest mean plasma drug concentrations occurred at the 0- to 4-h time point, the addition of another 2 time points between 0 and 4 h would further elucidate the actual time at which the drug reached its highest concentration or therapeutic levels. The same can be said about examining when the drug falls below therapeutic levels, thus illustrating the benefit of sample collection at 12 h. However, blood sampling is influenced by the body weight and therefore the circulating blood volume of the animal, and the volume of blood collected at a given point and collectively over a specific range of time has to be balanced with the minimal plasma sample needed for analysis at each time point. Unfortunately, in the current study, increasing the number of time points would have prohibitively reduced the volume of each blood sample. Furthermore, objective clinical assessment tools including blood chemistry and CBC analyses to evaluate effects on organ function were not performed in the current study.

In conclusion, the results of our study are a helpful starting point for providing guidance regarding selected analgesics in view of previously reported therapeutic levels in prairie dogs. Previously recommended doses for meloxicam in prairie dogs did not achieve therapeutic levels, suggesting that current published dosing guidelines may be subtherapeutic. In contrast, buprenorphine SR exceeded therapeutic levels beyond 96 h in both dosage groups. Additional research should be done to evaluate whether the dose might be reduced but still maintain therapeutic levels. The adverse injection site reactions might be minimized through careful tissue handling during injection, and no further adverse events were reported throughout the study. Further research should focus on evaluating other NSAID and opioids in standard and extended-release formulations, to provide clinicians with a wider range of drugs that can be used and with specific dose information for prairie dogs. In addition, because multimodal pain management has become the 'gold standard' and mainstay of pain management, future studies should examine the interaction between selected analgesics and analyze organ function to better understand potential risks of drug administration in this species. Future studies should also include the use of larger group sizes and additional sampling time points to determine statistical significance and compensate for interindividual variability.

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