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Comparison of Dexmedetomidine–Ketamine–Midazolam and Isoflurane for Anesthesia of Black-tailed Prairie Dogs (*Cynomys ludovicianus*)

Geoffrey R Browning,[1,*] David Eshar,[1] and Hugues Beaufrere[2]

Few studies evaluate anesthesia in black-tailed prairie dogs (*Cynomys ludovicianus*). Isoflurane inhalant anesthesia is used in this species most commonly, but injectable protocols are poorly described. Here we compared the physiologic effects, including anesthetic depth, vital signs, and hematologic changes, of anesthetic protocols using isoflurane or a combination of dexmedetomidine, ketamine, and midazolam in black-tailed prairie dogs. In a randomized, complete crossover study design, intact male black-tailed prairie dogs (*n* = 9; age, 6 mo) were anesthetized by using a combination of dexmedetomidine (0.25 mg/kg IM), ketamine (40 mg/kg IM), and midazolam (1.5 mg/kg IM). For reversal, atipamezole (0.15 mg/kg) and flumazenil (0.05 mg/kg) were administered 45 min after induction. For comparison, isoflurane was administered at 5% in 100% oxygen at 5 L/min in an anesthetic induction chamber, followed by maintenance isoflurane 2% in 2 L/min oxygen through a tight-fitting facemask for 45 min. Induction and recovery time, respiratory rate, heart rate, body temperature, SpO_2, indirect blood pressure, and reflexes were monitored every 5 min during the anesthetic period. Blood samples for venous blood gases, PCV, and refractometric total protein were obtained from the cranial vena cava at 5 min and 45 min. Both protocols appeared to achieve safe and effective anesthesia. Except for blood pressure, all vital signs differed between the 2 treatments. Isoflurane anesthesia resulted in a slightly longer induction and lower respiratory rate and body temperature but increased likelihood of absent reflexes. DKM anesthesia resulted in a faster induction and less hypothermia but also prolonged recovery and lower heart rate and SpO_2 readings. These findings suggest that isoflurane provides a more stable and consistent anesthetic plane, whereas dexmedetomidine–ketamine–midazolam anesthesia may be an effective alternative for short procedures that require fast induction and limited analgesia.

Abbreviations: DKM, dexmedetomidine–ketamine–midazolam; HR, heart rate; MAP, mean arterial blood pressure; RR, respiratory rate

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Black-tailed prairie dogs (*Cynomys ludovicianus*) are commonly used in research, housed in zoological institutions, and kept as companion exotic pets.[14,20] In research, prairie dogs have been used extensively as a model for gallstone formation and several infectious and zoonotic diseases.[3,14,16] In addition, they are considered a keystone species in prairie ecology.[17] Given their fractious nature, chemical immobilization or general anesthesia is often necessary for examination or diagnostic procedures in prairie dogs.[9,12] Inhalant anesthetic agents are most commonly used in anesthetic protocols; however, few studies evaluate injectable anesthetic agents in this species.[9,12]

Isoflurane is an anesthetic gas that is frequently recommended for use in prairie dog anesthesia.[23] Several studies evaluate isoflurane in this species, which is typically delivered via chamber or facemask due to difficulty in performing endotracheal intubation.[9,12,22] Inhalant anesthesia administered by facemask or induction chamber creates a significant occupational health concern for veterinary staff due to increased exposure to waste gases.[32-34] When equipment is not readily available, such as in the field setting, injectable anesthetic protocols may be desirable.[2,13,15,26]

Few studies have evaluated the efficacy and safety of injectable drugs for the induction and maintenance of anesthesia in prairie dogs. One study determined that a combination of xylazine (20 mg/kg IM) and ketamine (100 to 150 mg/kg IM) provided satisfactory anesthesia but had a 3.2% mortality rate when used in 63 prairie dogs.[29] To our knowledge, no recent studies investigate other injectable anesthetic agents in any prairie dog species, and most often, doses must be extrapolated from other rodent species, which can vary significantly. Because rodents appear to show higher risk for anesthetic or sedation-related death when compared with dogs and cats,[5] further research is necessary regarding the safety and efficacy of anesthetic protocols in rodent species.

To our knowledge, no studies have been published that evaluate the physiologic changes of injectable anesthetic protocols, including a combination of dexmedetomidine, ketamine, and midazolam (DKM), in black-tailed prairie dogs. Therefore, the objective of this study was to compare the physiologic effects including anesthetic depth, vital signs, and hematologic changes of anesthetic protocols using isoflurane or the injectable combination of DKM in black-tailed prairie dogs. Our hypothesis was that both isoflurane and DKM would achieve safe and effective anesthesia in black-tailed prairie dogs. Safe anesthesia

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[1]Department of Clinical Sciences, College of Veterinary Medicine, Manhattan, Kansas, and [2]Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada
[*]Corresponding author. Email: grbrowning@vet.k-state.edu

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was defined as no anesthetic-related deaths or lasting adverse perioperative complications on follow-up examination. DKM was hypothesized to be a suitable alternative to isoflurane and provide a stable anesthetic plane for anesthetic procedures lasting approximately 45 min; however, significant differences in the physiologic effects were expected between protocols.

Materials and Methods

This study was reviewed and approved by the IACUC at Kansas State University (IACUC no. 3952.3). Intact male black-tailed prairie dogs ($n = 9$; age, 6 mo; body weight: mean ± 1 SD, 714 ± 89 g; range, 600 to 894 g) were included in the study. The prairie dogs were housed in a 15 ft × 10 ft enclosure, where hay substrate, PVC pipes, and plastic crates were provided. Diet consisted of a commercial rodent pelleted diet, as well as fresh lettuce and other vegetables. At 1 wk prior to the study, each prairie dog was immobilized to undergo physical examination, packed cell volume, refractometric total protein, and plasma biochemistry profile to ensure that all animals were healthy. No significant abnormalities were identified during the physical examination or in clinical laboratory parameters, and each animal was individually color-marked and received an identification microchip. During the examinations of 3 animals, we tested preliminary anesthesia protocols using dexmedetomidine and ketamine alone up to their maximal doses (0.25 mg/kg IM and 40 mg/kg IM, respectively); none of these regimens achieved an adequate plane of anesthesia, which was defined as loss of all monitored reflexes and lack of response to test stimuli. Subsequent exams in 3 additional animals with the addition of midazolam in increasing doses (maximum, 1.5 mg/kg IM) to dexmedetomidine and ketamine allowed for the determination of an appropriate injectable protocol to be used in the current study.

For the current study, prairie dogs underwent anesthesia twice in a randomized crossover design. An online automated randomizing tool (Research Randomizer, www.randomizer.org) was used to randomize anesthetic protocols on each of the study days. A 3-d washout period was allowed between protocols. The first anesthetic protocol (DKM) consisted of intramuscular combined administration of dexmedetomidine (0.25 mg/kg; Dexdomitor, Zoetis, New York, NY), ketamine (40 mg/kg; Ketaset, Zoetis), and midazolam (1.5 mg/kg, Versed, Westward, Eatontown, NJ) into the epaxial musculature by using an insulin syringe with a 28-gauge needle. After 45 min of anesthesia, atipamezole (0.15 mg/kg; Antisedan, Zoetis) and flumazenil (0.05 mg/kg; Hikma Farmaceutica, Terrugem, Portugal) were administered intramuscularly. A second dose of flumazenil was administered when the animal had not regained a bright and alert mentation or was unable to ambulate by 1 h after administration of the first dose of reversal agents.

The second anesthetic protocol consisted of induction with isoflurane in 100% oxygen (5 L/min) that was delivered through a standard medium-sized induction chamber (28 in. × 10 in. × 8 in.). After gas induction, a tight-fitting facemask was placed and connected to a nonrebreathing circuit. Isoflurane was maintained at 2% in 100% oxygen (2 L/min) for 45 min, after which isoflurane was discontinued; oxygen was delivered until return of the righting reflex. All animals received a 40-mL subcutaneous bolus of lactated Ringers solution immediately prior to administration of reversal agents or cessation of isoflurane administration. Prairie dogs were placed in a crate for recovery and received active heat support with a forced-air patient warming system (Bair Hugger, Augustine Medical, Eden Prairie, MN).

Anesthetic induction time was monitored, which was defined as the time from intramuscular injection or the start of isoflurane administration to loss of righting reflex. In addition, palpebral, forelimb withdrawal, and hindlimb withdrawal reflexes were monitored every 5 min throughout the 45-min anesthetic period. Each reflex was scored as 0 (reflex present), 1 (reflex reduced), or 2 (reflex absent). Withdrawal was assessed by using hemostats to pinch a digit and observing the withdrawal response. The surgical plane of anesthesia was defined as loss of all monitored reflexes. Vital signs measured every 5 min were heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), rectal temperature, and indirect mean arterial blood pressure (MAP). HR and RR were auscultated by using a stethoscope. A commercial monitoring system (Waveline Touch, DRE Veterinary, Louisville, KY) was used to measure pulse oximetry on the right hind footpad and indirect MAP using oscillometric measurement with a size 2 cuff on the left hindlimb. Rectal temperature was monitored by using a digital thermometer. Recovery was defined as the return of all reflexes, including the righting reflex.

Blood samples were obtained 5 min after induction and after the 45-min anesthetic time point just prior to reversal or cessation of isoflurane administration. A 0.5-mL sample of blood collected from the cranial vena cava by using a 1.0-mL syringe and a 25-gauge needle was placed in a 0.5-mL lithium heparin tube. The sample was processed immediately by using an electrolyte and chemistry analyzer (iSTAT, Abaxis, Union City, CA). Each venous sample was analyzed for blood pH, P_{CO2}, P_{O2}, O_2, saturation, anion gap, and concentrations of bicarbonate, base excess, sodium, chloride, free calcium, free magnesium, glucose, lactate, BUN, creatinine, and total CO_2. A packed cell volume and refractometric total protein were also determined using standard hematocrit tube and a refractometer reading.

Statistical analysis. Statistical analysis was performed by using commercial software (R package version 3.1-121, R Foundation for Statistical Computing, Vienna, Austria). Longitudinal data analysis using linear mixed modeling was performed on the different outcome variables (anesthetic and hematologic variables) with time, treatments (DKM and isoflurane), and their interactions as fixed effects, and prairie dog as the random effect. Residual plots were used to assess linearity, homogeneity of variances, normality, and outliers. For normality assessment, quantile plots were performed on the residuals according to treatment group. Autocorrelation of the residuals over time was assessed by using the autocorrelation function. ANOVA was performed on the fixed effects, and posthoc comparisons were performed by using Tukey adjustment. Binary variables were analyzed by using a logistic mixed model with the same explanatory variables as mentioned earlier. Residuals were evaluated graphically. An α level of 0.05 was used for significance.

Results

All prairie dogs were stable throughout the perianesthetic period and experienced no adverse complications related to anesthesia during or after the conclusion of the study. Hematologic parameters from blood samples taken during the anesthetic period are presented in Table 1. Reflexes measured over the 45-min time period are presented in Table 2. Vital signs measured over the 45-min anesthetic period are presented in Table 3. Time to induction (mean ± 1 SD) was 2.31 ± 0.42 min in the isoflurane group and 0.91 ± 0.21 min for DKM. The isoflurane group had a significantly longer induction time (by about 84 ± 8 s; $P < 0.001$) when compared with DKM treatment. Time to recovery was 11 ± 8.17 min in the isoflurane group and 54.62 ± 30.49 min after DKM treatments. Isoflurane treatment was associated with a

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Table 1. Hematologic parameters (mean ± 1 SD) in prairie dogs (n = 9) anesthetized with dexmedetomidine-ketamine-midazolam or isoflurane in a crossover study design

	Dexmedetomidine–ketamine–midazolam		Isoflurane	
	5 min	45 min	5 min	45 min
Lactate (mmol/L)	12.1 ± 4.89	2.92 ± 0.87	8.17 ± 4.12	1.60 ± 0.54
pH	7.16 ± 0.08	7.40 ± 0.03	7.33 ± 0.06	7.36 ± 0.03
pCO_2 (mm Hg)	77.9 ± 10.2	67.7 ± 4.35	63.7 ± 8.22	72.3 ± 7.81
pO_2 (mm Hg)	35.2 ± 10.6	49.1 ± 20.7	124 ± 77.7	217.3 ± 133.3
Total CO_2 (mmol/L)	30.4 ± 5.37	44.4 ± 1.15	35.4 ± 4.62	43.3 ± 2.89
HCO_3 (mmol/L)	28.2 ± 5.22	42.2 ± 0.97	33.5 ± 4.54	41.1 ± 2.64
Base excess (mmol/L)	−0.5 ± 6.23	17.4 ± 1.09	7.59 ± 5.15	15.6 ± 2.5
sO_2 (%)	48.6 ± 17.3	72.7 ± 20.2	95.6 ± 3.08	99.1 ± 0.85
Na^+ (mmol/L)	143.8 ± 1.47	138.7 ± 1.25	140.4 ± 1.65	139.6 ± 1.54
K^+ (mmol/L)	4.49 ± 0.35	5.07 ± 0.86	4.48 ± 0.39	4.88 ± 0.43
Cl^- (mmol/L)	100.4 ± 1.67	92.2 ± 1.11	99.5 ± 1.20	98.6 ± 1.84
Anion gap (mmol/L)	22.1 ± 3.62	18.4 ± 7.47	15.4 ± 3.13	10.1 ± 2.01
Ionized Ca^{2+} (mg/dL)	1.25 ± 0.05	1.14 ± 0.03	1.19 ± 0.04	1.21 ± 0.08
Glucose (mg/dL)	146.2 ± 23.0	290 ± 32.40	145.8 ± 21.8	132.8 ± 10.7
BUN (mg/dL)	36.7 ± 5.20	33.7 ± 4.84	33.9 ± 6.45	34.8 ± 7.04
Creatinine (mg/dL)	0.64 ± 0.08	0.59 ± 0.10	0.54 ± 0.11	0.58 ± 0.11
Hct (%)	46.7 ± 2.27	45 ± 3.25	43.7 ± 3.18	40.1 ± 4.78
Hgb (g/dL)	15.9 ± 0.77	15.3 ± 1.11	14.8 ± 1.09	13.4 ± 1.20
PCV (%)	46.7 ± 2.41	43.9 ± 3.68	43.59 ± 3.28	37.9 ± 3.98
Refractometric total protein (g/dL)	6.61 ± 0.41	6.19 ± 0.70	6.32 ± 0.30	5.54 ± 0.34

All parameters except glucose and BUN differed significantly ($P < 0.05$) between the dexmedetomidine–ketamine–midazolam and isoflurane treatments.

significantly shorter recovery (by about 44 ± 10 min; $P = 0.004$) when compared with DKM treatment.

Significant differences in reflexes occurred between treatment groups. Compared with DKM and after controlling for anesthetic time, isoflurane treatment was more likely to lead to absence of palpebral reflex (odds ratio, 8.5; 95% CI, 2.7 to 26.2; $P < 0.001$). In addition, isoflurane treatment was more likely to lead to absence of a withdrawal reflex in both the forelimbs (odds ratio, 5.4; 95% CI, 1.4 to 20.4; $P = 0.012$) and hind legs (odds ratio, 12.7; 95% CI, 4.8 to 33.1; $P < 0.001$; respectively). Anesthesia time increased the likelihood of an absent reflex by about 5% per minute for isoflurane (odds ratio, 1.05; 95% CI, 1.01 to 1.10; $P = 0.019$) and 4% per minute for DKM (odds ratio, 1.04; 95% CI, 1.01 to 1.07; $P = 0.015$).

Except for MAP, all vital signs differed between the DKM and isoflurane treatment groups. The DKM treatment yielded significantly ($P < 0.001$) lower HR than isoflurane by about 65 ± 3 bpm (Figure 1). In the isoflurane group, the HR decreased over time ($P < 0.001$). Isoflurane was associated with a significant drop in RR by about 80 ± 3 when compared with DKM ($P < 0.001$) (Figure 2). Time did not have an effect on RR, which remained stable throughout anesthesia in both groups ($P = 0.89$). From 5 min through 25 min, SpO_2 was significantly lower for DKM treatment when compared with isoflurane treatment (all $P < 0.038$; Figure 3). There was a significant time×treatment interaction effect on SpO_2. Within the isoflurane treatment, SpO_2 was high and constant throughout anesthesia. Within the DKM treatment, the SpO_2 significantly increased after 35 min from the lowest value obtained at 5 min (all $P < 0.0064$). Rectal temperature was significantly ($P < 0.001$) lower during isoflurane anesthesia than DKM anesthesia by about 2 °F (Figure 4). In addition, body temperature decreased over time regardless of the anesthetic protocol ($P < 0.001$). Treatment and time did not have any effect on MAP (all $P > 0.49$; Figure 5).

Except for BUN and glucose, venous blood parameters differed between treatments (all $P > 0.068$). At all time points, pO_2 was higher for isoflurane than DKM (all $P < 0.014$). There was a significant time×treatment interaction effect on pO_2 ($P = 0.005$). In the DKM group, pO_2 started low and remained low throughout the treatment period, whereas in the isoflurane group, pO_2 started higher than for the DKM treatment ($P = 0.014$) and was still significantly ($P < 0.001$) higher at 45 min than at 5 min. At all time points, pCO_2 was higher for DKM than isoflurane (all $P < 0.024$). There was a significant ($P = 0.005$) time×treatment interaction effect on pCO_2. During DKM treatment, pCO_2 started high and remained high throughout the treatment period, whereas during isoflurane treatment, pCO_2 started lower than in the DKM treatment ($P < 0.001$) but were significantly higher at 45 min ($P < 0.001$), but still lower than in the DKM treatment ($P = 0.024$).

pH was significantly ($P < 0.001$) lower by 0.18 ± 0.01 in the DKM group. Time did not have an effect on pH ($P = 0.17$). Total CO_2, HCO_3, and base excess were higher at all time points for isoflurane treatment when compared with DKM (all $P < 0.001$). There were significant time×treatment interaction effects on total CO_2, HCO_3, and base excess ($P < 0.001$). In the DKM group, total CO_2, HCO_3, and base excess remained low throughout the treatment period. During isoflurane treatment, total CO_2, HCO_3, and base excess started higher ($P < 0.001$) than in the DKM group and remained significantly ($P < 0.001$) higher at 45 min than at 5 min.

At all time points, lactate concentration was higher for the DKM group than for isoflurane treatment (all $P < 0.001$). There was a significant ($P < 0.001$) time×treatment interaction effect

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Table 2. Percentage of prairie dogs (n = 9) with absent reflexes over 45 min while anesthetized with dexmedetomidine–ketamine–midazolam or isoflurane in a crossover study design

	Dexmedetomidine–ketamine–midazolam				Isoflurane			
Time (min)	Righting	Palpebral	Frontlimb withdrawal	Hindlimb withdrawal	Righting	Palpebral	Frontlimb withdrawal	Hindlimb withdrawal
0	100	50	87.5	62.5	100	78	78	67
5	100	87.5	100	87.5	100	78	89	56
10	100	100	100	87.5	100	100	100	78
15	100	100	100	75	100	100	100	100
20	100	100	100	62.5	100	100	100	100
25	100	100	100	50	100	100	100	100
30	100	75	100	50	100	100	100	100
35	100	75	75	25	100	100	100	100
40	100	50	75	0	100	100	100	100
45	100	0	25	0	100	100	100	88.9

Table 3. Vital signs[a] (mean ± 1 SD) in prairie dogs (n = 9) over 45 min while anesthetized with dexmedetomidine–ketamine–midazolam (DKM) or isoflurane in a crossover study design

	Group	0	5	10	15	20	25	30	35	40	45
Heart rate (bpm)	DKM	208.3 ± 39.0	172.5 ± 22.1	158.5 ± 24.2	150.8 ± 32.5	150.0 ± 24.1	143.75 ± 23.38	137.8 ± 19.2	134.5 ± 20.1	134.0 ± 18.0	130.0 ± 18.4
	Isoflurane	251.8 ± 22.9	242.2 ± 22.9	229.6 ± 26.7	231.8 ± 15.5	216.0 ± 17.7	205.33 ± 13.71	202.2 ± 15.6	195.6 ± 22.9	190.2 ± 18.8	189. 9 ± 16.3
Respiratory rate (breaths per min)	DKM	92.3 ± 25.9	91.0 ± 23.7	93.5 ± 22.8	110.3 ± 21.5	112.5 ± 19.2	112.5 ± 32.0	111.0 ± 17.5	115.0 ± 20.7	115.5 ± 20.3	100.0 ± 14.5
	Isoflurane	37.3 ± 15.5	31.1 ± 14.4	27.1 ± 11.1	29.3 ± 7.0	24.4 ± 8.8	22.2 ± 7.5	21.8 ± 6.7	19.6 ± 6.2	21.8 ± 5.3	19.1 ± 7.4
SpO_2 (%)	DKM	94.0 ± 6.0	88.5 ± 8.1	91.1 ± 4.5	92.6 ± 4.7	92.5 ± 2.8	92.9 ± 4.2	93.9 ± 4.9	94.9 ± 3.2	95.4 ± 2.3	95.6 ± 2.7
	Isoflurane	98.3 ± 1.4	98.6 ± 1.5	98.6 ± 1.2	98.8 ± 1.0	98.4 ± 2.1	98.3 ± 1.1	98.2 ± 0.8	99.0 ± 0.7	98.7 ± 0.9	98.9 ± 0.8
Temperature (°F)	DKM	100.2 ± 1.5	100.2 ± 1.5	100.0 ± 1.5	99.4 ± 1.7	99.0 ± 1.6	98.8 ± 1.4	98.3 ± 1.4	98.2 ± 1.4	97.8 ± 1.3	97.6 ± 1.3
	Isoflurane	98.5 ± 2.0	98.1 ± 2.5	97.6 ± 2.3	97.1 ± 2.2	96.7 ± 1.9	96.5 ± 1.7	96.4 ± 1.4	96.3 ± 1.1	96.2 ± 1.2	96.1 ± 1.2
Mean arterial pressure (mm Hg)	DKM	82.3 ± 37.1	107.9 ± 40.5	100.8 ± 43.0	86.4 ± 33.9	67.6 ± 20.1	94.4 ± 48.3	109.0 ± 39.4	100.3 ± 37.0	66.6 ± 33.4	94.4 ± 36.1
	Isoflurane	95.0 ± 4.3	85.3 ± 34.9	95.1 ± 30.7	109.1 ± 36.1	85.0 ± 26.3	77.5 ± 23.6	84.2 ± 30.6	93.0 ± 33.5	82.4 ± 30.3	75.3 ± 25.5

on lactate concentration. In the DKM animals, lactate remained high throughout anesthesia, whereas in the isoflurane group, lactates were significantly ($P < 0.001$) decreased at 45 min when compared with 5 min. Anion gap was higher at all time points for the DKM treatment when compared with the isoflurane treatment (all $P < 0.001$). There was a significant ($P < 0.001$) time×treatment interaction effect on anion gap. In the DKM treatment, anion gap started high and remained high throughout the treatment period, whereas for the isoflurane group, anion gap started lower ($P < 0.001$) than for the DKM treatment remained significantly lower ($P < 0.001$) at 45 min than at 5 min.

Discussion

In this study, 9 black-tailed prairie dogs were anesthetized in a randomized, complete crossover design using isoflurane and intramuscular administration of combined dexmedetomidine, ketamine, and midazolam as the randomized treatments. All prairie dogs were anesthetized and monitored for changes in reflexes, vital signs, and venous blood gas concentrations during each 45-min anesthetic period. Both protocols appeared to provide safe and effective anesthesia in black-tailed prairie dogs. According to the results of this study, DKM emerged as an option for the induction and maintenance of anesthesia in this species, particularly when isoflurane is undesirable or unavailable (such as under field conditions when gas anesthesia is not practical), and to avoid exposure to waste gases that are a harmful occupational hazard.[2,13,15,26,34]

In rodents, combination injectable protocols including ketamine and α2 agonists, such as the intramuscular DKM regimen we evaluated, are routinely used for chemical immobilization.[6,35] Dexmedetomidine is an α2 agonist that is reversible and provides analgesia, sedation, and muscle relaxation.[4,28] Ketamine is a dissociative, centrally acting NMDA receptor antagonist that also provides analgesia.[36] At their maximal tested doses, a DK combination did not achieve adequate anesthesia in pilot trials in this study; however, the addition of midazolam to the protocol resulted in longer, effective anesthesia. Midazolam, a benzodiazepine, is reversible and commonly used with minimal side effects for sedation in rodents.[36] To our knowledge, few reports feature the DKM combination in rodents.

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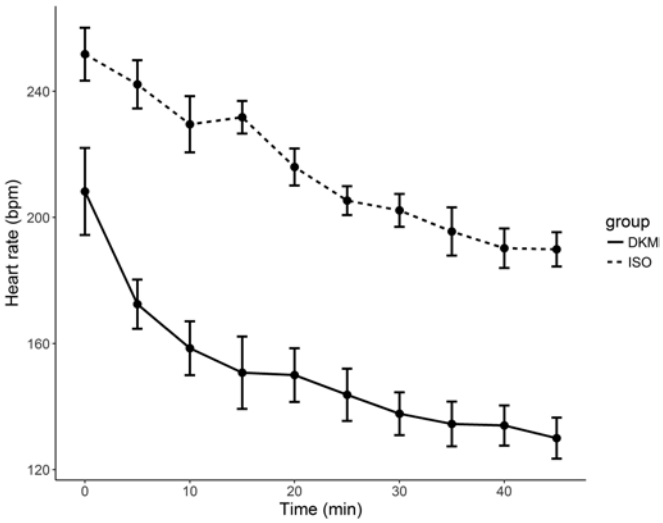

Figure 1. Heart rate (mean ± 1 SD) of black-tailed prairie dogs (n = 9) anesthetized with isoflurane (ISO) or dexmedetomidine–ketamine–midazolam (DKM) over 45 min in a randomized, crossover design. Heart rate was significantly ($P < 0.05$) lower in the DKM treatment group and decreased over time with isoflurane and DKM.

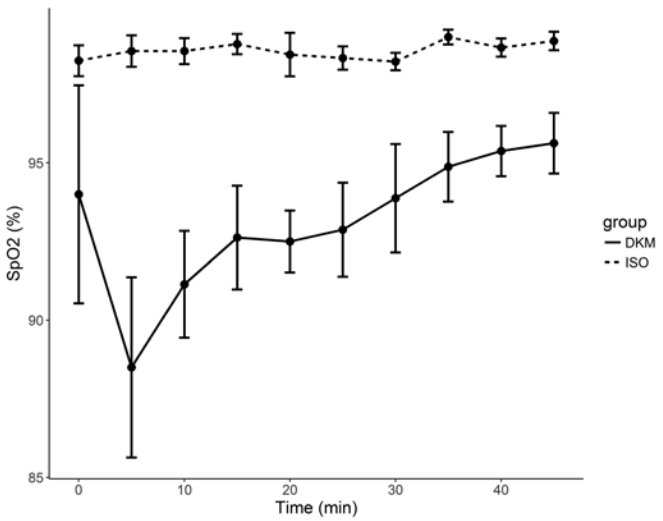

Figure 3. SpO_2 (mean ± 1 SD) of black-tailed prairie dogs (n = 9) anesthetized with isoflurane or dexmedetomidine–ketamine–midazolam over 45 min in a randomized, crossover design. SpO_2 was significantly lower in the DKM treatment group and increased over time; SpO_2 remained high in the isoflurane treatment group.

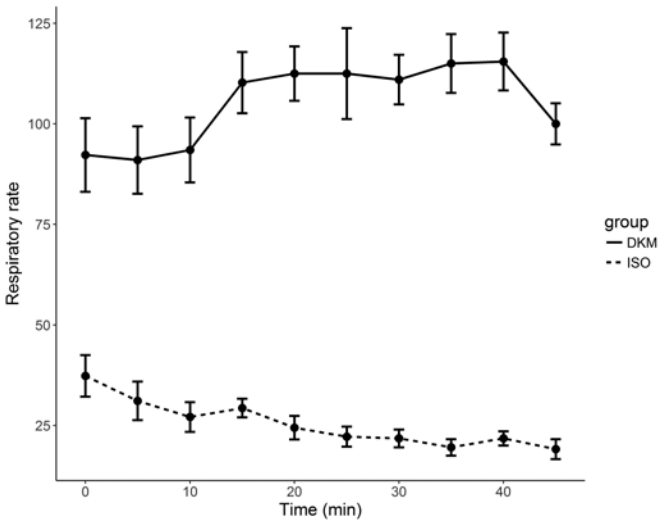

Figure 2. Respiratory rate (mean ± 1 SD) of black-tailed prairie dogs (n = 9) anesthetized with isoflurane or dexmedetomidine–ketamine–midazolam over 45 min in a randomized, crossover design. Respiratory rate was significantly lower in the isoflurane treatment group but remained stable over time in both groups.

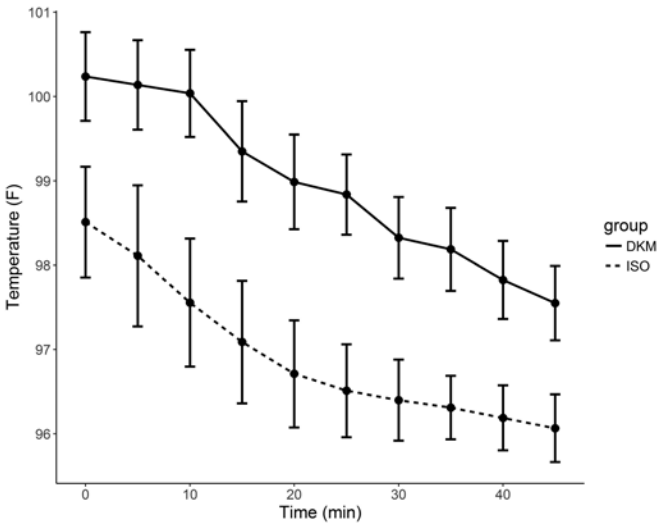

Figure 4. Temperature (mean ± 1 SD) of black-tailed prairie dogs (n = 9) over 45 min while anesthetized with isoflurane or dexmedetomidine–ketamine–midazolam in a randomized, crossover design. Rectal temperature was significantly lower in the isoflurane treatment, and temperature decreased over time in both treatments.

Injectable anesthetic protocols have been studied in rodents other than prairie dogs. α2 agonists including dexmedetomidine are often used in combination with ketamine and other drugs. In rats, a combination of ketamine (75 mg/kg IP) and dexmedetomidine (1 mg/kg IP) achieved anesthesia for a 30-min period; however, decreases in HR, RR, and SpO_2 were observed.[35] Another study in rats evaluated various anesthetic combinations with ketamine (75 mg/kg), including acepromazine (2.5 mg/kg), diazepam (5 mg/kg), medetomidine (0.5 mg/kg), midazolam (5 mg/kg), and xylazine (2.5 mg/kg).[25] In that study, α2 agonists with ketamine achieved the most stable and regular parameters in rats; however, there were significant differences between sexes.[25] A study in mice compared the effects of dexmedetomidine (0.5 mg/kg) and medetomidine (1 mg/kg) with ketamine (75 mg/kg) given intraperitoneally or subcutaneously.[6] Although loss of the righting reflex was noted, these protocols did not abolish pedal withdrawal reflexes in mice.[6] In guinea pigs, isoflurane and combinations of either ketamine (75 mg/kg) and xylazine (15 mg/kg) or medetomidine (0.2 mg/kg), midazolam (1 mg/kg), and fentanyl (0.025 mg/kg) were evaluated.[30] According to study findings, medetomidine–midazolam–fentanyl was the anesthetic of choice in guinea pigs; isoflurane was useful for short, nonpainful procedures; and ketamine–xylazine was not recommended for guinea pig anesthesia.[30] Another study involving various wild-caught rodents determined that a combination of ketamine (50 mg/kg) and medetomidine (1 mg/kg) provided effective, safe, and practical anesthesia for rodents that were live-trapped and anesthetized in a field setting.[13] Other field studies in rodent species include Richardson ground squirrels, which determined that xylazine (10 mg/kg) and ketamine (85 mg/kg) administered IM or SC induced effective surgical anesthesia.[26] In wild-caught Cape

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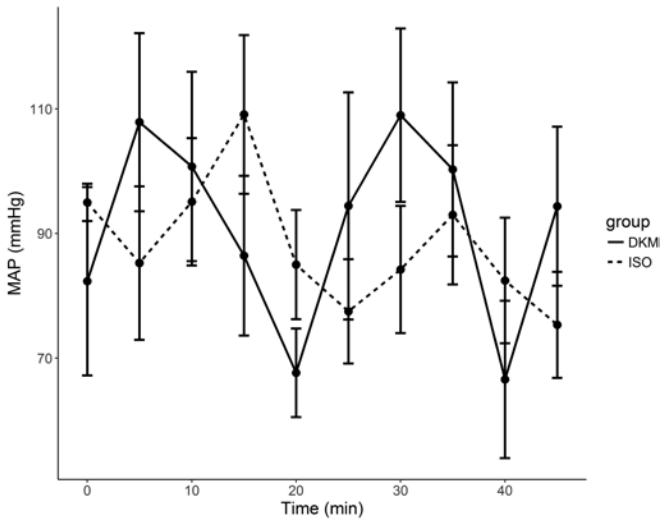

Figure 5. Mean arterial blood pressure (mean ± 1 SD) of black-tailed prairie dogs (n = 9) anesthetized in a randomized, crossover design with isoflurane or dexmedetomidine-ketamine-midazolam over 45 min. There was no effect of treatment or time observed on indirect MAP.

ground squirrels, a combination of medetomidine (67.6 µg/kg), ketamine (13.6 mg/kg), and buprenorphine (0.5 µg/kg) achieved surgical anesthesia with a rapid recovery following atipamezole (0.23 mg/kg) administration under field conditions.[15] In free-ranging alpine marmots, combinations of xylazine (3 to 20 mg/kg) and ketamine (40 to 60 mg/kg), medetomidine (0.25-0.5 mg/kg) and ketamine (35 to 70 mg/kg), or xylazine (3 to 10 mg/kg) and zolazepam-tiletamine (15 to 20 mg/kg) were effective and safe for short or long-term surgery during a field project; however, differences were noted between seasons.[2]

To our knowledge, only one previous study[29] has evaluated injectable anesthetic protocols in a prairie dog species. In that study, a combination of xylazine (5 to 20 mg/kg IM) and ketamine (100 to 150 mg/kg IM) achieved a surgical plane of anesthesia for approximately 90 min in black-tailed prairie dogs.[29] Acepromazine (0.5 mg/kg IM) and ketamine (50 mg/kg IM) achieved heavy sedation but not surgical anesthesia.[29] In that study, xylazine–ketamine provided a smoother induction, better muscle relaxation, longer duration of anesthesia, and smoother recovery than the acepromazine–ketamine combination. However, 2 prairie dogs (3.2%) died due to anesthetic complications associated with xylazine and ketamine; anesthetic parameters, hematologic changes, and vital signs were not reported.[29]

Isoflurane anesthesia in prairie dogs is commonly recommended.[20,22] Studies have evaluated cardiac parameters, venous blood gas analytes, and the effects of recumbency on physiology parameters in black-tailed prairie dogs under isoflurane anesthesia.[9,11,12] The results of our current study support the use of isoflurane for anesthesia of prairie dogs and suggest that it offers advantages and disadvantages over the injectable DKM protocol we evaluated here. In general, one potential disadvantage of inhalant anesthesia is lack of analgesia.[36] Because of the fractious nature of prairie dogs, we elected to use chamber induction rather than a facemask. Induction chambers are a widely accepted method for use in rodents and other animals; however, they expose personnel to potentially harmful waste anesthetic gases when chambers are opened.[32] Flushing the induction chamber has been suggested as an option to reduce waste gas exposure but requires modification to the chamber system.[37]

A study similar to our current study compared isoflurane and a combination of dexmedetomidine (0.015 mg/kg) and ketamine (4 mg/kg) in chinchillas (*Chinchilla lanigera*).[10] In that study, both protocols provided effective anesthesia in chinchillas, and there were no differences in induction time, HR, RR, or body temperature. However, isoflurane administration led to more rapid recovery times in chinchillas,[10] similar to the present study in prairie dogs. The differing results between chinchillas and prairie dogs perhaps are due to differences in species physiology and the protocols used. It is important to note that significantly higher doses of dexmedetomidine and ketamine and the addition of midazolam were necessary to achieve similar plane of anesthesia in prairie dogs in this study when compared with the regimens used in chinchillas. This difference demonstrates that extrapolation of anesthetic doses and drug combinations between species or contexts may not be effective. Species-specific research may be necessary to determine safe and effective anesthetic protocols.

In the present study, induction time was significantly longer with isoflurane; this outcome was most likely associated with the use of an anesthetic induction chamber. However, all prairie dogs were induced within 3 min of the start of isoflurane administration, and effective anesthesia was achieved. In chinchillas, induction time between did not differ between isoflurane and dexmedetomidine–ketamine; however, anesthesia was induced more directly by using a facemask for the isoflurane treatment in that study.[10] Recovery time was prolonged in prairie dogs that received the DKM treatment in our current study. The most likely contributing factors to this delay include hypothermia and insufficient drug reversal. Hypothermia, which occurred late during anesthesia in all DKM animals in this study, can slow the metabolism of drugs including anesthetic agents.[21] The use of ketamine, which is a nonreversible drug, might have contributed to the prolonged recovery in DKM-anesthetized prairie dogs; however, this effect was not observed in the preliminary pilot trials without the addition of midazolam to the tested injectable protocol. Inadequate reversal and renarcotization could explain the prolonged recovery, and all 9 prairie dogs required a second dose of flumazenil (0.05 mg/kg) during the recovery period. These results indicate that prairie dogs anesthetized with DKM may require a flumazenil dose of 0.1 mg/kg and postanesthesia monitoring for at least 1.5 h during recovery.

In this study, there were significant differences in the anesthetic depth and vital signs between the isoflurane and DKM treatments. Isoflurane administration resulted in a more stable anesthetic plane, as demonstrated by the increased likelihood of absent palpebral and withdrawal reflexes throughout the anesthetic period. All prairie dogs in the isoflurane group experienced loss of all measured reflexes by 15 min after induction, and in most animals these effects lasted for the remainder of the 45-min anesthetic period. The DKM protocol did not provide a surgical plane of anesthesia, defined as loss of all monitored reflexes, in all prairie dogs. In most DKM-treated animals, anesthesia lasted 35 min or less; by 40 min, all prairie dogs anesthetized with DKM had regained a hindlimb reflex response. These findings suggest that isoflurane may provide a more consistent, predictable anesthesia over time and across subjects than DKM at the tested doses.

In the present study, bradycardia occurred within 5 min of induction with DKM and lasted throughout the anesthetic period. In the DKM group, HR was significantly lower than for isoflurane and decreased over time. We expected this finding given the use of dexmedetomidine, an α2 agonist. This class of drug acts on adrenergic receptors and causes peripheral vasoconstriction, leading to increased vascular resistance followed by subsequent decreases in HR and cardiac output.[24]

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Dose-dependent cardiovascular changes are observed with α2 agonist administration in small animals.[19,24] HR in our prairie dogs decreased steadily throughout the 45-min anesthetic period with the isoflurane treatment. In addition, isoflurane administration leads to cardiovascular depression due to vasodilation and negative inotropy.[1]

In our study, RR remained stable over time in both treatment groups; however, decreased RR was seen throughout the anesthetic period with the isoflurane treatment. Despite this, SpO_2 remained above 98.2% ± 0.8% with isoflurane, which we expected given the supplementation of oxygen in the isoflurane group only. Prairie dogs in the DKM group were tachypneic, but they experienced decreased pO_2, sO_2, and SpO_2 and respiratory acidosis. Significantly decreased SpO_2 in the DKM treatment group was noted within 5 min of induction; after this period, SpO_2 gradually increased over the remainder of anesthesia. SpO_2 was measured by using a pulse oximeter, which can produce inaccurate readings when tissue perfusion is poor, such as during vasoconstriction.[7] Regardless, DKM was associated with decreased SpO_2 throughout the 45-min period. Arterial blood gas evaluation is necessary to accurately assess oxygenation. Respiratory depression and hypoxemia have occurred in other species receiving combination injectable anesthetic protocols that include dexmedetomidine.[10,31] These findings support the addition of supplemental oxygen when using this injectable DKM protocol in prairie dogs.

Body temperature was significantly lower with isoflurane administration and decreased gradually over the 45-min anesthetic period with both isoflurane and DKM anesthesia. Normal body temperature in captive black-tailed prairie dogs is reported to be 97.2 to 97.9 °F.[16] Most animals anesthetized with isoflurane were hypothermic according to this range by 20 min, and all experienced hypothermia during the anesthetic period. In the DKM treatment, only 2 animals were hypothermic. Hypothermia in both treatments might reflect impaired thermoregulatory mechanisms under anesthesia, which can lead to heat loss.[8] Given these results, we recommend active thermal support with both anesthesia protocols, especially isoflurane, in prairie dogs. Oxygen as a carrier agent for isoflurane might have contributed to the greater heat loss that was observed in that treatment group because it is a cool, dry gas. In addition, isoflurane causes dose-dependent vasodilation, which facilitates cutaneous heat loss.[8] α2 agonists may protect against cutaneous heat loss and preserve core body temperature due to peripheral vasoconstriction and redistribution of blood centrally.[8,31] Given the results of our current study, DKM may be advantageous over isoflurane for anesthesia of black-tailed prairie dogs when thermal support is unavailable.

Neither anesthetic protocol that we evaluated significantly affected MAP in prairie dogs. These findings could be associated with the method of indirect MAP measurement, which has not been validated in prairie dogs to our knowledge. Both isoflurane and dexmedetomidine can result in changes in blood pressure, but we noted no trends or significant changes in blood pressure in the present study. These findings suggest that oscillometric measurement may not be reliable in prairie dogs. Direct measurement of arterial blood pressure is considered the 'gold standard' and may be necessary to determine the effects of each anesthetic protocol in black-tailed prairie dogs in future studies.

Several differences in hematologic parameters were observed with the DKM and isoflurane treatments. Venous pCO_2 was greater with DKM throughout the anesthetic period, and respiratory acidosis developed over time in the isoflurane group. These increases in pCO_2 can be attributed to hypoventilation, which is similar to the results of a previous study evaluating the effects of isoflurane on venous blood gas analytes.[12] In that study, hypoventilation and subsequent respiratory acidosis was speculated to cause decreased venous pH due to isoflurane administration.[12] Our DKM-treated animals initially demonstrated acidemia, which resolved over time. Decreased pH with DKM can be attributed to both respiratory acidosis and metabolic acidosis, as indicated by the decreased bicarbonate concentration and negative base excess.

Lactate was higher at all time points in the DKM group, and the isoflurane group experienced decreasing lactate concentration over time. Elevated lactate is associated with decreased oxygen delivery or increased oxygen demand.[27] In prairie dogs anesthetized with DKM, lactic acidosis can be attributed to decreased oxygen delivery due to dexmedetomidine and its cardiovascular effects. Increased lactate during DKM treatment can explain the higher anion gap, which quantifies unmeasured anions including lactate.[18] In this study, isoflurane administration led to a decreasing lactate concentration over time. Hypothermia, which can result in decreased metabolism, might explain this trend and may have contributed to decreased lactate production in that group. An elevated initial lactate concentration in prairie dogs might be due to manual restraint prior to and excitement during the prolonged induction, which could have increased oxygen demand. Minimizing handling stress and increasing oxygenation may be beneficial during the induction of anesthesia in black-tailed prairie dogs.

Limitations of the present study include a small sample size, which could have led to type II error in some parameters. However, previous studies evaluating anesthesia in other species have used similar sample sizes, including for chinchillas ($n = 8$), dogs ($n = 8$ to 11), and guinea pigs ($n = 16$).[4,10,30] Future studies may include a larger sample size with a similar randomized, crossover study design. Female prairie dogs might be included in future studies to determine the presence of any sex-associated differences, as demonstrated in rats.[25] We did not monitor food intake or fecal output after anesthetic protocols in our animals. In chinchillas, fecal output and food intake were reduced for 3 d after anesthesia in animals that received dexmedetomidine–ketamine but not isoflurane.[10] We monitored our prairie dogs for 1 wk after anesthesia, and no overt adverse effects were noted. Future studies could include quantitative monitoring of some parameters, such as fecal output or food intake, in black-tailed prairie dogs to further characterize the physiologic effects of each protocol.

The findings of the present study suggest that both DKM and isoflurane are safe and effective protocols for anesthesia in black-tailed prairie dogs, and each protocol has advantages and disadvantages regarding its resulting physiologic effects. Isoflurane provided a more reliable and consistent anesthetic plane for 45 min and a relatively faster recovery. However, DKM achieved effective anesthesia for as long as 35 min, with a prompt induction and less hypothermia than isoflurane administration. These findings suggest that DKM may be a suitable alternative for anesthesia in black-tailed prairie dogs for short procedures that may be painful and to eliminate exposure to waste gases. Further research is necessary to determine an appropriate injectable protocol for complete anesthesia lasting longer than 35 min in prairie dogs.

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