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Comparison of Dexmedetomidine–Ketamine with Isoflurane for Anesthesia of Chinchillas (*Chinchilla lanigera*)

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The objective of this study was to compare isoflurane with a combination of dexmedetomidine and ketamine, administered intramuscularly, for anesthesia in chinchillas (*Chinchilla lanigera*). In a prospective, complete crossover study, adult chinchillas (*n* = 8; age, 2 to 5 y) were anesthetized with a combination of dexmedetomidine (0.015 mg/kg IM) and ketamine (4 mg/kg IM). Atipamezole (0.15 mg/kg) was injected subcutaneously 45 min after dexmedetomidine–ketamine administration. For comparison, anesthesia also was induced and maintained with isoflurane in 100% oxygen, delivered by facemask. Anesthetic and physiologic parameters were recorded during each anesthesia, including various reflexes, heart rate, respiratory rate, body temperature, and SpO_2. Food intake, fecal output, and body weight were recorded daily for 6 d after each anesthetic trial. Induction time, heart rate, respiratory rate, and body temperature did not differ significantly between the 2 anesthetic protocols. Recovery times were shorter and SpO_2 was higher in animals that received isoflurane delivered in 100% oxygen. Food intake and fecal output were reduced in the dexmedetomidine–ketamine group for as long as 3 d after anesthesia, whereas isoflurane had no signifcant effect on food intake or fecal output. Both anesthetic protocols provided effective anesthesia in chinchillas. However, when anesthetized with dexmedetomidine–ketamine, chinchillas received room air and became hypoxemic. Future studies are needed to evaluate the effect of oxygen supplementation on anesthetic recovery and on the recovery of food intake and fecal output in chinchillas.

Abbreviation: DK, dexmedetomidine–ketamine.

Chinchillas are used extensively in research to study otitis media, hearing loss, and ototoxicity.[1,11,19,25] In addition, chinchillas are becoming increasingly popular as companion animals and, therefore, are more frequently presented for veterinary care. Common diseases of chinchillas include dental disease, gastrointestinal disorders, and ocular disorders.[13,14] Chemical immobilization is often required to perform diagnostic (for example, radiography, CT), therapeutic, or experimental procedures.[3,5,7,21] Research regarding the efficacy and safety of anesthetic protocols in chinchillas is limited and currently recommended protocols rely largely on extrapolation from other species or anecdotal reports.[13,21,27]

Isoflurane is used routinely in chinchillas for the induction and maintenance of anesthesia. A study investigating the echocardiographic effects of isoflurane in chinchillas found significant effects on several echocardiographic parameters, but no complications or other side effects were reported.[12] Isoflurane typically is delivered by facemask to chinchillas, given that endotracheal intubation is technically challenging and therefore not performed routinely.[10,21] However, using a facemask increases the risk of exposure of the veterinary staff to waste gases, which is a significant occupational health concern.[20,23] Therefore, alternative anesthetic protocols that reduce waste-gas exposure are desired, such as exclusively using injectable anesthetic drugs for induction and maintenance of anesthesia. Intravascular access is challenging to obtain in conscious chinchillas, and thus parenteral, nonvascular protocols provide the most accommodating route for anesthesia induction and maintenance.[14] Only one study in chinchillas has investigated the effects of various injectable anesthetics: a combination of medetomidine (0.06 mg/kg) and ketamine (5 mg/kg) was compared with other parenteral protocols.[14] Although anesthesia was successful with this protocol, the authors reported respiratory and cardiac depression in the animals. Furthermore, although atipamezole is commonly administered in clinical and research settings to promote rapid recovery and prevent complications, such as hypothermia, it was not used in the cited study.[14]

To our knowledge, no studies have been published that assess the effects of anesthetic protocols on recovery of food intake and fecal output in chinchillas. The objective of this study was to compare the anesthesia induced in chinchillas by using either dexmedetomidine and ketamine or isoflurane and to evaluate the effects of both anesthetic protocols on subsequent food intake, fecal output, and body weight.

Materials and Methods

This study was approved by the University of Wisconsin's animal care and use committee. Eight chinchillas (4 male, 4 female; age, 2 to 5 y; body weight [mean ± SD], 0.69 ± 0.05 kg) were obtained from a commercial breeder (R and R Chinchillas, Jenera, OH). Animals were housed in a climate-controlled room with a 12:12-h light:dark cycle (lights on, 0700 to 1900), room temperature of 21 to 23 °C, and relative humidity of 40% to 55%. The chinchillas were maintained in individual cages (0.69 m × 0.69 m × 0.46 m; 6-cage Rabbit Housing Unit, Allentown, Allentown, NJ) with perforated plastic excreta pans. Each cage contained a plastic hide box as well as cardboard tubes and a

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piece of natural manzanita wood for foraging. The opportunity to exercise and socialize in a playpen (1.8 m × 0.9 m), which contained a dust bath, was provided at least once weekly. The chinchillas received a commercial pelleted rabbit diet (MannaPro Rabbit pellets, MannaPro Products, Chesterfield, MO) and tap water from a ball-tipped water bottle. All chinchillas were acclimated to the housing conditions for at least 4 wk prior to starting the experiments.

Each chinchilla underwent anesthesia twice in a randomized complete crossover design, with a washout time between anesthetic episodes of at least 7 d. Dexmedetomidine (0.015 mg/kg; Dexdomitor, Pfizer Animal Health, New York, NY) and ketamine (4 mg/kg; Ketamine Hydrochloride Injection, Hospira, Lake Forest, IL) were administered intramuscularly as a single injection in the epaxial musculature by using an insulin syringe with an attached 28-gauge hypodermic needle; 45 min after dexmedetomidine–ketamine (DK) administration, atipamezole (0.15 mg/kg; Antisedan, Pfizer Animal Health) was administered subcutaneously to reverse the effects of dexmedetomidine. Animals in the DK group breathed room air during the experiment, and no flow-by oxygen was provided. The second anesthetic protocol consisted of induction with isoflurane in oxygen (2 L/min) by using an out-of-circle isoflurane vaporizer and manual restraint. A tight-fitting facemask was used and connected to a modified Jackson–Rees breathing circuit. Isoflurane was set to 4% for induction until there was an absence of the righting reflex, after which it was lowered to 2% for the duration of anesthesia (1 L/min oxygen flow rate). Isoflurane was delivered for a total of 45 min and then discontinued. The circuit was flushed with oxygen, and then oxygen delivery by facemask was continued until the animal's righting reflex returned. A water-based eye lubricant was instilled in the eyes of all chinchillas after the induction of anesthesia.

Anesthetic induction time and time to surgical anesthesia was recorded. Measured reflexes included righting, palpebral, forelimb withdrawal, and hindlimb withdrawal. Reflexes were scored on a scale of 0 to 2, with 0 indicating a present reflex, 1 indicating a reduced reflex, and 2 indicating an absent reflex. Anesthetic induction time was defined as time to loss of the righting reflex, which was assessed by placing the chinchillas in dorsal recumbency and observing whether they could return to normal quadrupedal position. Withdrawal reflexes were assessed by pinching a digit with hemostats and observing a reflex response. Surgical anesthesia was defined as the complete loss in all measured reflexes (that is, all scores of 2). During the 45-min anesthetic period, heart rate, respiratory rate, SpO_2 determined by pulse oximetry of a hindlimb digital pad (model 8500, Nonin Medical, Minneapolis, MN), and rectal temperature were measured at 5-min intervals. Heart rate and respiratory rate were monitored by auscultation. After reversal with atipamezole or discontinuation of isoflurane delivery, the chinchillas were monitored until recovery from anesthesia was complete, measured by the return of all reflexes.

Food intake, fecal output, and body weight were measured daily at the same time each day, starting 24 h prior to anesthesia (day 0) and for 6 d afterward. The leftover food and feces found in each cage were collected, sorted, and measured manually.

Statistical analysis. Commercial software (SigmaPlot 12.5, Systat Software, San Jose, CA) was used to perform the data analysis. The data were evaluated for normal distribution by using the Shapiro–Wilk test. The physiologic data (heart and respiratory rates, SpO_2, rectal temperature) were compared by averaging 3 values to obtain a single mean value for each 15-min period of anesthesia. Data that were not normally distributed were reported as median, interquartile range, and range. Normally distributed data were reported as mean ± 1 SD. Two-way repeated-measure ANOVA was used to assess the effects of time and anesthetic protocol on physiologic parameters (heart and respiratory rates, SpO_2, rectal temperature) as well as body weight, food intake and fecal output. The Holm–Sidak method was used for posthoc pairwise comparisons when significant differences were found between groups. The anesthetic induction and recovery times were analyzed by using the Wilcoxon signed-rank test. A P value less than 0.05 was considered statistically significant.

Results

Data regarding anesthetic induction and recovery are summarized in Table 1. Both anesthetic protocols resulted in rapid induction, and animals were maintained at surgical anesthesia for 45 min. Time to loss of evaluated reflexes did not differ between protocols, but the time to return of the forelimb withdrawal reflex was a median of 5 min in the DK group compared with a median of 3 min in the isoflurane group ($P = 0.03$). There was a trend toward statistical significance ($P = 0.06$) for faster return of the righting reflex in chinchillas anesthetized with isoflurane. Total time for recovery of all 4 reflexes after anesthesia was 3 to 15 min for the DK group compared with 1 to 6 min for the isoflurane group.

Heart rate did not differ between the 2 anesthetic protocols. Heart rate in the isoflurane group did not change significantly over time (Figure 1 A) but was decreased in the DK group at 30 and 45 min compared with 15 min. Respiratory rate decreased over the course of anesthesia, but only the decrease at 45 min in the isoflurane group was statistically significant ($P = 0.02$); there was a trend toward statistical significance ($P = 0.06$) for a decrease in respiratory rate between the 15- and 45-min time points in the DK group (Figure 1 B).

SpO_2 was higher in the isoflurane group ($P = 0.05$), which received 100% oxygen throughout anesthesia. Chinchillas in the DK group, which did not receive supplemental oxygen, were hypoxemic throughout the anesthetic period. SpO_2 did not change significantly over time in either treatment group (Figure 1 C).

Compared with that at 15 min, rectal temperature was decreased at the 45-min time point in the DK group ($P < 0.01$; 2.8 °C), whereas there was a trend toward statistical significance ($P = 0.06$) in the isoflurane group for the decrease in temperature between the same 2 time points. By 45 min, all animals in the isoflurane group and 5 of the 8 animals in the DK group were hypothermic (physiologic range, 36.1 to 37.8 °C).[15]

Food intake was significantly different between groups for 3 d after anesthesia. Specifically, food intake in the DK group was decreased ($P < 0.001$) compared to baseline and to that of the isoflurane group (Figure 2 A). The greatest decrease in food intake occurred during the first 24 h, when mean food intake was reduced by 61% ± 25% compared with the preanesthetic baseline (Figure 2 A). Food intake did not change significantly in the isoflurane group after anesthesia.

For 2 d, fecal output was reduced ($P < 0.001$) in the DK group compared with the isoflurane group, with a trend toward statistical significance between groups ($P = 0.06$) for as long as 3 d. Compared to the preanesthetic baseline, fecal output was significantly ($P < 0.01$) reduced for 3 d in the DK group (Figure 2 B), with the greatest decrease (50% ± 30%) during the first 24 h. Fecal output did not change significantly in the isoflurane group after anesthesia. No significant differences in body weight were found within or between anesthetic protocols.

Table 1. Anesthetic induction and recovery parameters in chinchillas (n = 8) anesthetized with either dexmedetomidine–ketamine or isoflurane in a crossover study

	Dexmedetomidine–Ketamine			Isoflurane			
	Median	IQR	Range	Median	IQR	Range	*P*
Induction							
Righting reflex absent	2.0	2.0-3.0	1.0-5.0	2.0	2.0-2.0	1.0-3.0	0.44
Palpebral reflex absent	3.0	2.3-3.8	1.0-5.0	2.5	2.0-3.0	1.0-3.0	0.31
Forelimb withdrawal reflex absent	2.5	2.0-4.0	2.0-4.0	4.0	2.0-5.75	1.0-15.0	0.31
Hindlimb withdrawal reflex absent	3.5	2.3-4.8	2.0-15.0	5.0	2.25-30.0	1.0-40.0	0.16
Recovery							
Righting reflex present	5.0	4.0-8.0	4.0-15.0	4.0	2.0-5.75	1.0-6.0	0.06
Palpebral reflex present	4.0	1.5-7.5	1.0-15.0	3.0	2.0-5.0	1.0-6.0	0.38
Forelimb withdrawal reflex present	5.0	3.3-7.5	3.0-15.0	3.0	2.0-3.75	1.0-5.0	0.03
Hindlimb withdrawal reflex present	3.5	2.3-7.5	1.0-15.0	3.0	2.0-4.75	1.0-5.0	0.22

IQR, interquartile range
For induction, data are recorded as time (min) after induction by injection or facemask. For recovery, data are recorded as time (min) after antagonist injection or cessation of gas administration at 45 min after induction of anesthesia.

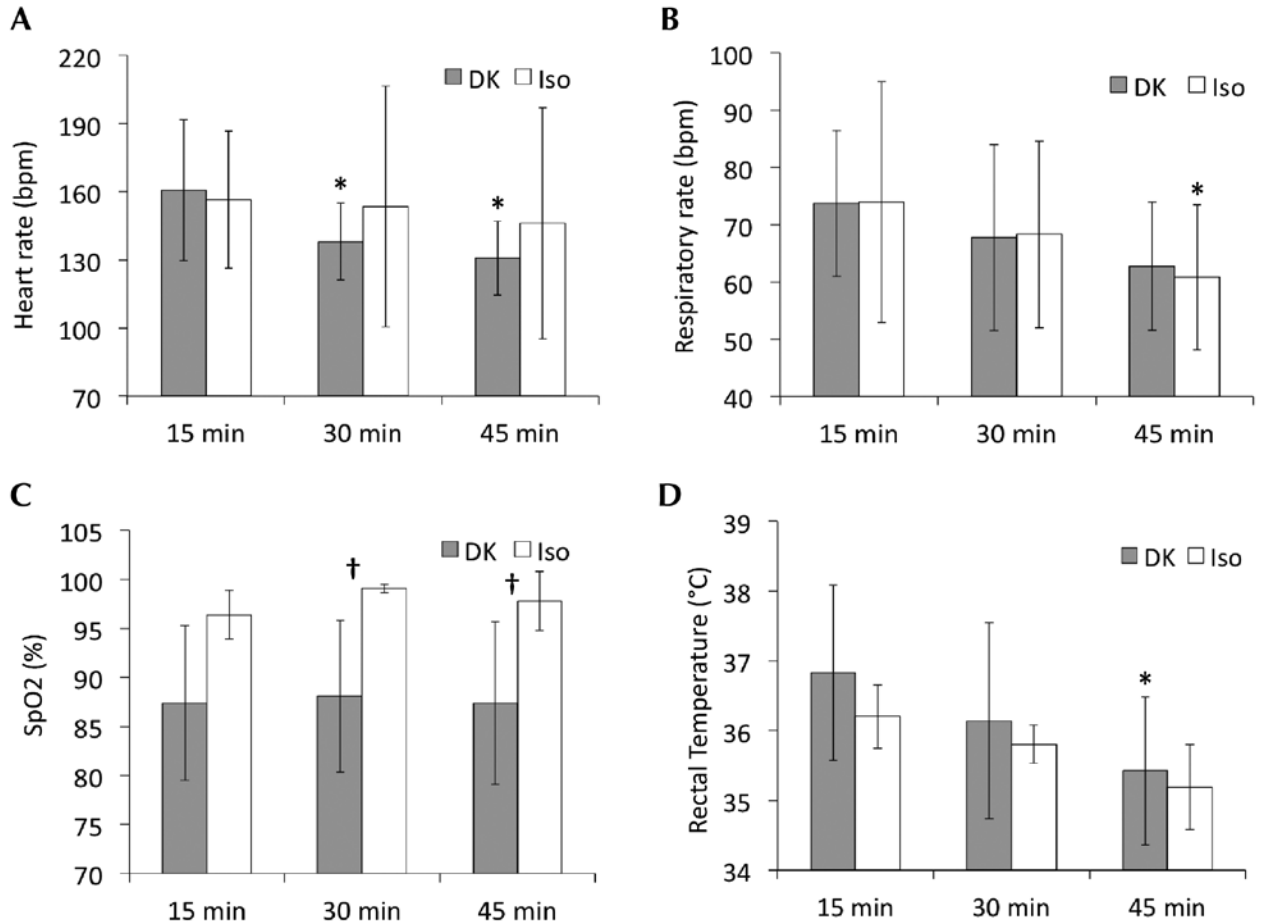

Figure 1. (A) Heart rate, (B) respiratory rate, (C) SpO2, and (D) rectal temperature (mean ± 1 SD) of chinchillas (n = 8) anesthetized with isoflurane (Iso) or dexmedetomidine–ketamine (DK) in a complete crossover design. *, Value differed significantly ($P < 0.05$) from that at 15 min within the same protocol; †, values differed significantly ($P < 0.05$) between anesthetic protocols at the same time point.

Discussion

The evaluated anesthetic regimens of DK and isoflurane resulted in safe and effective anesthesia for the chinchillas used in this study. Induction times were rapid and smooth with both protocols. However, recoveries were slightly longer and food intake and fecal output were decreased in the DK group compared with the isoflurane group.

α_2-Adrenergic receptor agonists, such as medetomidine and dexmedetomidine, are used frequently in rodent anesthesia and typically are combined with ketamine or with an opioid and benzodiazepine.[13,14,17,27] Despite their ease of use, the administration of α_2-adrenergic receptor agonists is not without consequence. Across species, α_2-adrenergic receptor agonists are well known to stimulate peripheral α_2 adrenergic receptors in

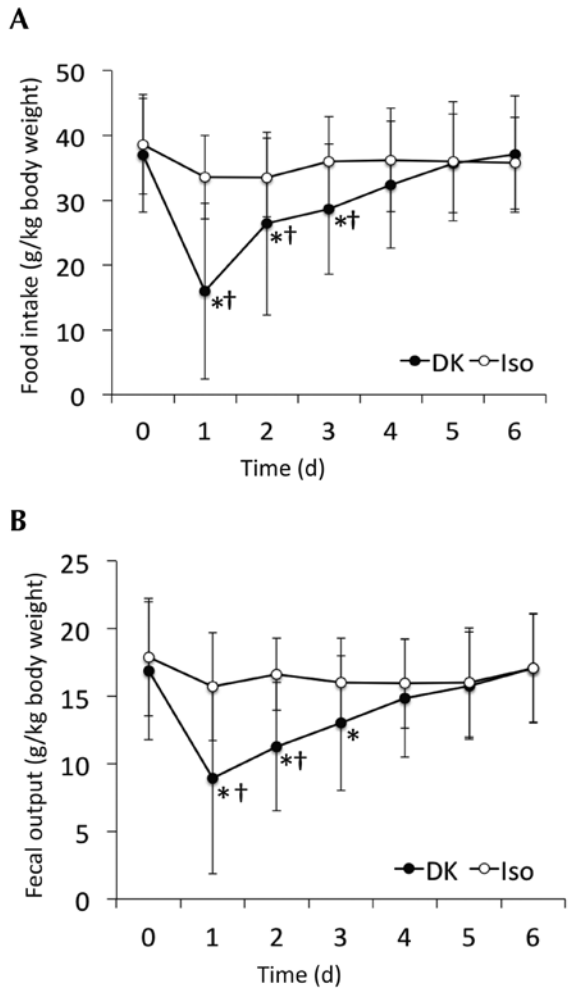

Figure 2. (A) Food intake and (B) fecal output (g/kg body weight; mean ± 1 SD) of chinchillas (n = 8) before 0 d and after anesthesia with isoflurane (Iso) or dexmedetomidine–ketamine (DK) in a complete crossover design. *, Value differed significantly ($P < 0.05$) from that at 15 min within the same protocol; †, values differed significantly ($P < 0.05$) between anesthetic protocols at the same time point.

the arterioles, leading to vasoconstriction and increased peripheral vascular resistance. This response can increase afterload and decrease heart rate and cardiac output. In addition, when animals anesthetized with α_2-adrenergic receptor agonists breathe room air, hypoventilation can decrease the oxygen saturation of hemoglobin.[22] In a study performed in rats, dexmedetomidine–ketamine anesthesia significantly decreased oxygen saturation at 15 min after induction and led to a 20% decrease in heart rate, 33% decrease in respiratory rate, and 20% decrease in oxygen saturation over 30 min.[26] In contrast, respiratory rates in our current study decreased by only 3.4% on average, and heart rate decreased by only 14.4% over the first 30 min after the administration of DK. The more profound effects reported in rats might reflect the higher dosages of dexmedetomidine (1 mg/kg) and ketamine (75 mg/kg) used.[26]

The range of heart rate in the chinchillas anesthetized in the current study (range, 130 to 220 bpm; mean, 170 ± 22 bpm) was comparable to the HR in another study investigating the effects of isoflurane on echocardiographic measurements in chinchillas.[16] Heart rates did not differ between the 2 evaluated anesthetic protocols in our study. Our results show that the effect of DK on heart rate is comparable to that of isoflurane anesthesia, but heart rate decreased over time in the DK group. In contrast, chinchillas anesthetized with medetomidine and ketamine showed only an initial bradycardic episode during induction, after which heart rate remained stable over time.[14]

Respiratory rates were similar with both anesthetic protocols in our study and are similar to those in chinchillas anesthetized with medetomidine–ketamine.[14] After 45 min of anesthesia, respiratory rates were still within the reported physiologic range for chinchillas (40 to 80 bpm).[17] In addition, in the absence of thermal support, chinchillas were hypothermic after 45 min of either DK or isoflurane anesthesia. Hypothermia can have several deterimental effects, including delayed drug metabolism and excretion of anesthetic and analgesic drugs, hypotension, and delayed recovery.[8] In a study in dogs, time to extubation was increased by approximately 6 min for every 1 °C loss in body temperature.[15] Therefore the provision of supplemental heat may be helpful in counteracting the anesthesia-associated decrease in body temperature in chinchillas. The delivery of isoflurane uses oxygen as a carrier gas, and the oxygen is delivered as cool, dry gas through the facemask. The delivery of oxygen and isoflurane by mask did not appear to have a negative effect on the rectal temperature in the isoflurane group.

One of the limitations of the current study is the lack of an established minimum alveolar concentration of isoflurane in chinchillas. This parameter is defined as the minimal alveolar concentration of inhalant anesthetic that prevents gross purposeful movement in 50% of animals when a noxious stimulus is applied, such as a toe clamp.[9] At 1.5 times the minimal alveolar concentration, 95% of patients have no gross purposeful movement in response to a noxious stimulus, and surgical anesthesia will be achieved. In our case, the forelimb and hindlimb toe-pinch reflexes were present, albeit sluggish, throughout much of the 45-min anesthetic period. We based our vaporized isoflurane concentration on the published minimal alveolar concentration of 1.3% in rats and therefore equilibrated the isoflurane concentration to 2% in an attempt to achieve 1.5 times the minimal alveolar concentration in chinchillas.[18] Extrapolating the rat data to chinchillas likely was inappropriate in this case. Consequently, the time to loss of the hindlimb toe-pinch reflex varied markedly among our chinchillas, which might have received an incorrect dose of isoflurane. The minimal alveolar concentration of isoflurane in chinchillas warrants further investigation.

In another study investigating anesthetic protocols in chinchillas, a completely reversible protocol (midazolam–fentanyl–medetomidine) was compared with medetomidine–ketamine anesthesia.[14] The ability to completely reverse injectable anesthetics has been shown to limit the risk of hypothermia and various negative effects on respiratory and cardiovascular systems in guinea pigs.[14] However, by using the partially reversible DK combination in chinchillas, we noted no abnormally delayed recoveries when atipamezole was administered 45 min after the administration of DK.

Chinchillas anesthetized with isoflurane only showed a nonsignificant decrease in food intake after anesthesia. This finding is similar to a study in mice, where food intake after isoflurane anesthesia decreased by 10% on the first day after anesthesia and then returned to baseline by day 2.[6] In contrast, food intake after anesthesia with DK was significantly decreased in our chinchillas. This result might reflect a direct depressive effect of one or both of the drugs, thus decreasing normal feeding behavior. African green monkeys (*Chlorocebus aethiops*) have also shown reduction in food intake at 24 and 48 h after ketamine administration.[24] In addition, all of the chinchillas

anesthetized with DK received atipamezole, an α_2 adrenergic receptor antagonist, which has been shown to reduce food intake in dogs,[2] and yohimbine, another α_2 adrenergic receptor antagonist, reduces food intake in mice.[4] Therefore, we cannot rule out a similar appetite-decreasing effect of atipamezole in our chinchillas, and this drug may be responsible for at least part of the marked reduction in food intake and fecal output after anesthesia. Although a direct effect of dexmedetomidine, ketamine, or atipamezole might cause the pronounced decrease in food intake in the chinchillas in our study, the hypoxemia during anesthesia with DK might have contributed to this effect.

Despite the significant decrease in food intake in the chinchillas anesthetized with DK, no significant change in body weight was detected. These findings suggest that measuring food intake after anesthesia is a more sensitive parameter than is measuring body weight.

Chinchillas anesthetized with DK breathing room air had lower blood oxygenation levels than animals anesthetized with isoflurane delivered in 100% oxygen. The hypoxemia in the DK group is comparable to results of a study in chinchillas anesthetized with medetomidine and ketamine without supplemental oxygen.[14] Without oxygen support, hypoventilation leads to a decrease in SpO2. Additional concerns are the lack of validation of pulse oximetry in chinchillas as well as the possible effect of dexmedetomidine-induced peripheral vasoconstriction on the accuracy of pulse oximetry.[12] The observed hypoxemia might be avoided by providing oxygen delivered by facemask during anesthesia. However, despite the more severe and longer lasting decrease in food intake in chinchillas anesthetized by using DK compared with isoflurane, all animals recovered completely and without complications.

In conclusion, both evaluated anesthetic protocols resulted in safe and effective anesthesia in chinchillas, as defined by rapid induction, stable surgical anesthetic depth, and rapid recovery. However, the animals anesthetized with DK did not receive supplemental oxygen and developed hypoxemia. Food intake and fecal output were unaffected by isoflurane anesthesia but decreased significantly for up to 3 d after anesthesia with DK. These self-limiting side effects of DK anesthesia in chinchillas should be considered when selecting anesthetic protocols, and appropriate monitoring should occur in the anesthetic and postanesthetic period. The differences between the anesthetic protocols that we noted here indicate that, overall, isoflurane is a safer anesthetic protocol because it resulted in fewer perianesthetic physiologic changes, more rapid recovery times, and fewer postanesthetic side effects than the DK protocol. However, in terms of convenience and substantially decreased occupational risk, the DK protocol is preferable, but supplemental oxygen should be provided.

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