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# Comparison of Ketamine–Xylazine and Ketamine–Dexmedetomidine Anesthesia and Intraperitoneal Tolerance in Rats

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**We compared ketamine–xylazine (K, 100 mg/kg; X, 10 mg/kg) and ketamine–dexmedetomidine (K, 75 mg/kg; D, 1.0 mg/kg) for their ability to produce anesthesia, their tissue tolerance, and the reversibility of their effects by atipamezole (1.0 mg/kg) after intraperitoneal administration to Wistar Han rats. Both anesthetic combinations led to a comparable level of anesthesia over a 30-min period. However, the administration of KD led to a 20% decrease in heart rate, 33% decrease in respiratory rate, and a 20% decrease in peripheral oxygen saturation from baseline levels. Intraperitoneal administration of saline and both anesthetic combinations was associated with mild transient increases in serum ALT and AST concentrations in the absence of histomorphologic findings in liver. Muscle and tissue necrosis at the intraperitoneal injection sites correlated with increases in serum creatine kinase concentrations in rats given KD or KX; these increases were more severe in the KX group than the KD group. Compared with KX, intraperitoneal administration of KD offered better local tolerance and anesthesia of similar quality and depth.**

**Abbreviations:** CK, creatine kinase; KD, ketamine–dexmedetomidine; KX, ketamine–xylazine.

Ketamine is a noncompetitive, centrally acting, dissociative general anesthetic that provides amnesia, analgesia, and immobility.[33] Ketamine typically is used as an adjunct anesthetic, due to its limited ability to provide adequate skeletal muscle relaxation.[7,10,42] When combined with xylazine, the combination is regarded as the agent of choice for rodent injectable anesthesia.[10,38,44] The popularity of ketamine–xylazine (KX) is mainly due to its supplemental effects (that is, analgesic properties, muscle relaxation, and sedation).[43] Although the combination of KX provides relatively safe anesthesia, this anesthetic combination has demonstrated variability in providing a surgical plane of anesthesia in rodents with a failure rate of 20% to 40%.[10,25] Furthermore, the use of the KX anesthetic combination as an anesthetic in rodents has limitations, including a prolonged induction time and mediocre local tolerance when administered intramuscularly.[20,38] In light of these limitations, the small muscle mass of rodents, and ease of intraperitoneal administration, injectable anesthetics such as KX typically are given intraperitoneally in these species.[36] The intraperitoneal administration of injectable anesthetics in rodents provides rapid absorption, at a rate 25% to 50% of that of intravenous administration, thereby enabling rapid anesthetic induction.[20,36]

Dexmedetomidine is an $\alpha_2$-adrenoreceptor agonist similar to medetomidine but lacks the pharmacologically inactive enantiomer levomedetomidine, making dexmedetomidine 2 times more potent in anesthetic efficacy than medetomidine and 40 times more potent than xylazine.[2,3,28] Extensive studies have been conducted to evaluate the use of dexmedetomidine in humans, cats, and dogs.[2,4,7,11,13,16,19,27,32] In veterinary medicine, the advantages of combining dexmedetomidine and ketamine have been due to the combination's predictable, rapid, and smooth induction and maintenance of anesthesia. In addition, dexmedetomidine provides excellent muscle relaxation and analgesia for surgical procedures.[2] Furthermore, administration of atipamezole, an $\alpha_2$-adrenoreceptor antagonist, provides rapid reversal of anesthetic effects and leads to rapid recovery. In rats, IM tolerance was significantly higher for ketamine–medetomidine than for ketamine only.[39] The discontinuation of medetomidine production for veterinary use in the United States has prompted the investigation of dexmedetomidine, a dextrorotary enantiomer of medetomidine, as a replacement in rodent anesthetic protocols.[28] Currently, there is paucity of information describing the effects of substituting dexmedetomidine for medetomidine in rodent anesthetic protocols; therefore, we sought to compare the anesthetic and physiologic effects of these 2 anesthetic agents.

The present study was undertaken to evaluate the sedative and physiologic effects of ketamine–xylazine (K, 100 mg/kg; X, 10 mg/kg) and ketamine–dexmedetomidine (K, 75 mg/kg; D, 1.0 mg/kg) when administered intraperitoneally; the pain and discomfort and subsequent peritoneal tissue and muscle damage after intraperitoneal administration of these combinations; the effects of these anesthetic combinations on liver and muscle clinical biochemistry values; and the ability of subcutaneous atipamezole to reverse the anesthetic effects of KX and KD.

## Materials and Methods

**Animals.** Male Wistar Han rats (*Rattus norvegicus*, Crl:Wi(Han); $n$ = 40; age, 3 to 4 mo; weight, 434 ± 32 g) were obtained from Charles River Laboratories (Wilmington, MA). The rats were housed 2 per cage on corncob bedding (Shepherd's Cob, Shepherd Specialty Papers, Quakertown, PA) in polycarbonate cages and were maintained under climate-controlled conditions of a 12:12-h light:dark cycle, 10 to 15 air changes hourly, 20 to 25 °C (72 ± 4 °F), and relative humidity of 30% to 70%. Rats were

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acclimated for at least 2 wk prior to study initiation. All rats received a standard pelleted rodent diet (Lab Diet Certified Rodent Diet, no. 5002, PMI Nutrition International, St Louis, MO) and reverse-osmosis-purified water offered ad libitum.

**Anesthetic protocol.** To prepare the KX solution, 4.0 mL ketamine HCL (100 mg/mL; Ketaset, Fort Dodge Animal Health, Fort Dodge, IA), 2.0 mL xylazine (20 mg/mL; Anased, Akorn, Decatur, IL), and 2.0 mL sterile saline (Hospira, Lake Forest, IL) were mixed in a sterile vial. KX solution was administered intraperitoneally at a dose of 100 mg/kg ketamine and 10 mg/kg xylazine.[12,40]

To prepare the KD solution, 2.25 mL ketamine (100 mg/mL, Fort Dodge Animal Health), 5.50 mL dexmedetomidine (0.50 mg/mL; Dexdomitor, Pfizer Animal Health, New York, NY), and 1.25 mL sterile saline (Hospira) were mixed in a sterile vial (Abbot Laboratories). KD solution was administered intraperitoneally at 75 mg/kg ketamine and 1.0 mg/kg dexmedetomidine.[12,40]

**Reversal of anesthesia.** Atipamezole solution was prepared by mixing 0.50 mL atipamezole (5 mg/mL; Antisedan, Pfizer Animal Health) with 9.5 mL sterile saline (Hospira) in a sterile vial. Atipamezole solution was administered at a dose of 1.0 mg/kg SC.[12,40]

**Experimental procedure.** All described procedures were reviewed and approved by Roche Animal Care and Use Committee. Procedures were performed in an AAALAC-accredited facility. One day prior to study initiation, rats were weighed by using an electronic precision balance scale (Mettler Toledo, Columbus, OH), and the intraperitoneal and subcutaneous injection sites were shaved to allow for easier identification at necropsy. Prior to the initial injection, the probe of a handheld pulse oximeter (model 8500AV, Nonin, Plymouth, MN) was placed on the digits of the right or left hindlimb for approximately 3 min to allow acquisition of baseline heart rate and $SpO_2$ levels. Once anesthetic administration was completed and righting reflex was lost, heart rate and $SpO_2$ were monitored continuously recovery; respiratory rate was assessed by visualization of spontaneous breaths.

The data in this manuscript were generated from 2 replicate experiments, with the only difference between experiments being the bleeding time points. All data were combined for statistical analysis. In experiment 1, rats ($n$ = 23) were randomly assigned to receive either KX and atipamezole ($n$ = 5), KD and atipamezole ($n$ = 6), or sterile saline (controls; $n$ = 12, 6 animals per group). Control groups consisted of rats that received saline (5 mL/kg IP and SC) or saline (5 mL/kg IP) and atipamezole (1.0 mg/kg SC at 30 min after the intraperitoneal saline injection). In experiment 2, rats ($n$ = 17) were randomly assigned to receive either KX and atipamezole or KD and atipamezole ($n$ = 6 rats per treatment group); control rats ($n$ = 5) received sterile saline (5 mL/kg IP) and atipamezole (1.0 mg/kg SC). The 30-min duration of anesthesia was selected based on the average time of rodent surgical procedures at our institution.

The rubber stoppers on each bottle were wiped once with an alcohol swab prior to needle puncture, to prevent contamination of solutions. All intraperitoneal injections were given into the lower right quadrant of the abdomen by using a 25-gauge, 5/8-in. needle attached to a 1.0-mL or 3. 0-mL syringe (Becton Dickinson, Franklin Lakes, NJ), with the rat restrained in the Trendelenburg position.[10,14] All subcutaneous injections were given at the base of the skin fold between shoulder blades by using a 25-gauge, 5/8-in. needle attached to a 3.0-mL syringe (Becton Dickinson). Volumes administered intraperitoneally ranged from 0.86 to 2.20 mL, and those given subcutaneously ranged from 1.50 to 2.40 mL. Each rat was restrained and anesthetized by the same investigator (DW).

After all intraperitoneal injections, the behavioral reaction of each rat to the initial injection was graded based on a scale of 0 (no reaction) to 4 (kicks at syringe and attempts to bite handler, with vocalization; Figure 1).[41] The same investigator (DW) scored the reaction of all animals. Once the righting reflex was lost, the rats were placed in lateral recumbency on top of a circulating hot-water blanket (Heat Therapy Pump, Gaymar Industries, Orchard Park, NY) covered with a polypropylene fluid-resistant pad throughout the anesthetic period and recovery. Sterile ocular lubricant (Puralube Vet Ointment, Dechra Veterinary Products, Overland Park, KS) was administered to both eyes. A pulse-oximetry probe was positioned on the digits of the right or left hindlimb. Depth of anesthesia was assessed every minute until reflexes were lost and then every 5 min for 30 min. The parameters of chemical immobilization recorded every 5 min were ear pinch, palpebral, and pedal withdrawal reflexes.[10] Atipamezole (1.0 mg/kg SC) was administered after 30 min of anesthesia. The return of reflexive responses was assessed every minute; with assessment of physiologic parameters (heart rate, respiratory rate, and $SpO_2$) every 5 min after administration of reversal until the return of reflexes (primarily the righting reflex) was noted.

**Blood collection and analysis.** Serial blood samples were collected from unanesthetized rats by using 25-gauge × 5/8-in. needles attached to 1.0-mL tuberculin syringes (Becton Dickinson). In experiment 1, blood was collected at 3, 6, 12, 24, and 48 h after anesthetic injection. In experiment 2, blood was collected at 0, 3, 12, and 48 h after anesthetic injection. A total of 0.80 mL of blood was collected at each time point from the jugular vein. Blood samples were collected in serum separator gel tubes (Becton Dickinson) and centrifuged within 10 min of collection at 4307 × $g$ for 5 min at 4 °C for serum separation. The serum was frozen at −70 °C until analyzed within 1 wk of collection. Serum samples were thawed and analyzed by using a Modular Analytics System (Roche Diagnostics, Indianapolis, IN) for the determination of serum ALT, AST, and creatine kinase (CK) concentrations.

**Histopathology.** Rats were euthanized by $CO_2$ asphyxiation at 48 h after injection. Tissues collected for routine histomorphologic evaluation included the injection sites (with full thickness sections of the abdominal wall), liver, pancreas, mesentery, mesenteric lymph nodes, spleen, and gastrointestinal tract. Tissues were processed by routine paraffin infiltration, and 5-µm sections were prepared and stained with hematoxylin and eosin. The product of the width by the depth of muscle necrosis was used to quantify this finding at the injection sites. In addition, this parameter and necrosis of the subcutaneous adipose tissue, inflammation, and hemorrhage were graded from 0 (no findings) to 5 (severe).

**Statistical analysis.** Statistical analysis of the physiologic data, surface of muscle necrosis at the injection sites, and serum concentrations of ALT, AST, and CK levels were performed by using Prism (version 5.02; GraphPad Software, La Jolla, CA). The serum concentrations of ALT, AST, and CK of rats in the KX and KD groups at each time point were fitted to a 1-way ANOVA model and compared with those of rats in the saline groups. Statistical significance was defined as a $P$ value of less than 0.05. For each group of rats, data are presented as mean ± 1 SD.

## Results

**Behavioral response to intraperitoneal injection.** In both experiments, the KX and KD groups had significantly ($P < 0.05$)

| Score | Reaction to injection |
|---|---|
| 0 | None |
| 1 | Demonstrates minor signs of discomfort (for example, flinching) |
| 2 | Attempts to escape restraint and move away from handler |
| 3 | Kicks at syringe, attempts to bite handler, without vocalization |
| 4 | Kicks at syringe, attempts to bite handler, with vocalization |

**Figure 1.** Grading scale for assessment of rats' reactions to intraperitoneal injection.

higher behavioral response scores to the intraperitoneal injections than did the saline group (Figure 2). The administration of KX led to significantly ($P < 0.05$) higher reaction scores than did KD.

**Onset of anesthesia.** The onset of anesthesia was indicated by the loss of the righting, ear pinch, and pedal reflexes and was characterized by muscle relaxation in both the KX and KD groups within 6 min of injection in both experiments. The actual time of onset of anesthesia did not differ significantly between KX and KD groups. The KD group demonstrated more rapid ($P < 0.05$) loss of palpebral reflexes than did the KX group; however, there was no significant difference in the time to loss of pedal reflex between groups (Table 1). In the KX group, the pedal reflex was not lost in 2 of 11 (18%) rats during the 30-min anesthetic period, indicating the lack of a surgical plane of anesthesia.

**Cardiopulmonary effects.** Heart rates, respiratory rates, and $SpO_2$ were evaluated to determine differences at each time point over a 30-min period after anesthetic administration. In both experiments, heart rates were significantly ($P < 0.05$) lower in the KD group than in the KX group, beginning 10 min after anesthetic administration and remaining below baseline levels until 20 min after anesthetic reversal (Figure 3). Respiratory rates in KX rats were significantly lower at 25 min after anesthetic induction compared with baseline levels. Anesthetic induction with KX led to a significantly ($P < 0.05$) lower respiratory rate 25 min after anesthetic induction when compared with KD (Figure 4). $SpO_2$ in the KD group was significantly ($P < 0.05$) lower than in the KX group at 15 min after anesthetic induction and remained below baseline levels until reversal of anesthesia (Figure 5).

**Recovery from anesthesia.** The time to return of the righting, pedal, palpebral, and ear pinch reflexes was significantly longer in the KD group (49.6 ± 22, 14.6 ± 9.9, 25.6 ± 12.1, and 25.6 ± 12 min, respectively) compared with the KX group (22.0 ± 9.3 min, $P = 0.0178$; 4.0 ± 1.3 min, $P = 0.0464$; 5.40 ± 3.7 min, $P = 0.0032$; and 10.4 ± 9.0 min, $P = 0.0265$, respectively).

**Serum chemistry and histopathology.** Compared with the concentrations at baseline and 48 h, serum ALT and AST concentrations were higher at the 6-, 12-, and 24-h time points in all groups, including rats administered saline (Figure 6 A and B). KX led to significantly ($P < 0.05$) higher levels of ALT and AST at 12 and 24 h after anesthetic administration, compared with KD. These findings occurred in the absence of a histomorphologic correlate in the liver.

Compared with the concentrations at baseline and 48 h, serum CK concentrations increased ($P < 0.05$) in rats given KX, KD, or saline, with the maximal serum CK concentrations 3 h after dosing (Figure 7). The increase in serum CK concentrations at 3 h was of greater magnitude in rats given KX than in those that received KD. At 12 h after anesthesia, serum CK concentrations in all groups were the same as baseline levels. These findings correlated with acute muscle necrosis at the intraperitoneal injection site in rats of all 3 test groups. The severity of muscle necrosis was greater ($P < 0.05$) and its surface was larger ($P < 0.05$) for rats that received KX (6.0 ± 1.4 $mm^2$) or KD (0.5 ± 1.6 $mm^2$) than in rats given saline (0.01 ± 4 $mm^2$). The surface of muscle necrosis was larger ($P < 0.05$) for KX than for KD.

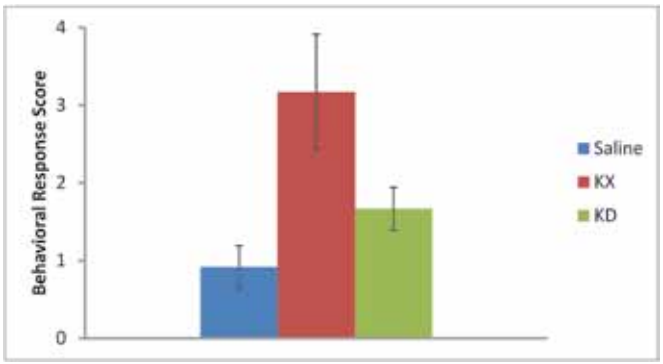


**Figure 2.** Rats' reactions to intraperitoneal injection was significantly ($P < 0.05$) greater for KX than for KD and significantly ($P < 0.05$) greater for KD than saline.

The surface area of muscle necrosis at the subcutaneous injection site was similar and did not differ significantly between saline (0.1 ± 1.8 $mm^2$) and atipamezole (0.5 ± 2.0 $mm^2$) groups. Findings at the intraperitoneal (Figure 8 A and B) and subcutaneous injection sites (Figure 9) consisted of inflammation and adipose necrosis, which were interpreted as secondary to or extensions of muscle necrosis. There were no treatment-related histomorphologic changes in the other tissues examined. Furthermore, there were no particular changes in the liver or at the peritoneal surface underlying the intraperitoneal injection site.

## Discussion

The primary aim of this study was to determine whether intraperitoneal KD compared with KX maintained a surgical depth of anesthesia for at least 30 min. Our results indicated that KX and KD led to comparable levels of anesthesia. Although KX failed to provide a surgical depth of anesthesia in 2 rats, the anesthetic combination provided adequate muscle relaxation in the remaining rats throughout the anesthetic period. Administration of KD led to bradycardia, respiratory depression, and subsequent hypoxemia, whereas KX resulted in a short period of respiratory depression. In addition, both anesthetic combinations were associated with poor local tolerance characterized by the expression of momentary pain and discomfort on administration, localized tissue damage consisting predominantly of muscle necrosis, and a transient increase in serum ALT, AST, and CK levels. The subcutaneous administration of atipamezole led to the rapid return of physiologic parameters to baseline levels in both anesthetic groups; however, anesthetic reversal was longer for rats receiving KD than for those in the KX group. This study provides evidence that the intraperitoneal administration of KD has better local tolerance than that of KX yet provides anesthesia of similar quality and depth.

In this study, the objective assessment and grading of behavioral reaction scores was higher for KX than for KD in both experiments. We speculate that these elevated reaction scores may be due to the low pH of KX (pH = 4.86) and KD (pH = 4.60).[41] Although both of these anesthetic combinations are acidic, it appears that the lower dose of ketamine in the KD combination resulted in lower behavioral reaction scores. Our findings are similar to previous studies, which have demonstrated that the low pH of ketamine administered alone compared with in combination with other anesthetics results in pain, discomfort, and localized tissue inflammation when

**Table 1.** Time (min, mean ± SE) to onset of loss of reflex responses after administration of KX or KD.

| | Righting reflex (P = 0.1459) | Ear pinch reflex (P = 0.0791) | Palpebral reflex (P = 0.0317) | Pedal reflex (P = 0.3671) |
|---|---|---|---|---|
| KX | 3.4 ± 1.7 | 3.2 ± 1.8 | 4.1 ± 2.3 | 4.4 ± 1.9 |
| KD | 6.3 ± 4.2 | 1.6 ± 1.0 | 1.6 ± 1.0 | 3.9 ± 2.0 |

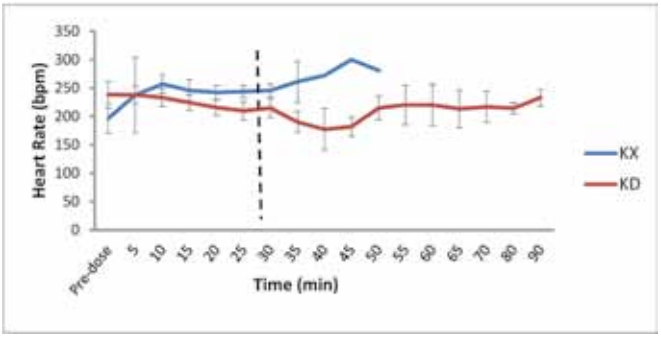


**Figure 3.** Heart rate (bpm) after administration of KX and KD. Anesthesia was reversed (dotted vertical line; atipamezole, 1.0 mg/kg) at 30 min after the administration of anesthetic.

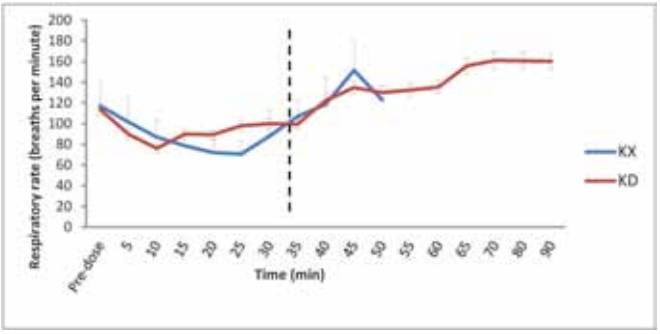


**Figure 4.** Respiratory rate (breaths per minute) after administration of KX and KD. Anesthesia was reversed (dotted vertical line; atipamezole, 1.0 mg/kg) at 30 min after the administration of anesthetic.

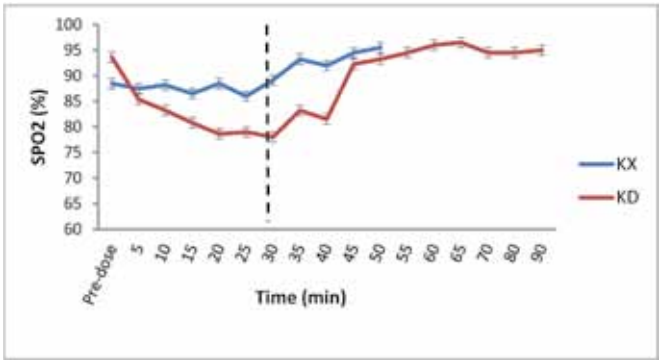


**Figure 5.** Peripheral oxyhemoglobin saturation (%) after administration of KX and KD. Anesthesia was reversed (dotted vertical line; atipamezole, 1.0 mg/kg) at 30 min after the administration of anesthetic.

administered intramuscularly.[20,36,41] The poor local tolerance of anesthetic combinations comprising ketamine contributed to the shift from the intramuscular to the intraperitoneal route of administration in rodents.[36] Our current study demonstrated that the intraperitoneal administration of anesthetic combinations comprising ketamine also caused muscle damage. The intraperitoneal and subcutaneous injection of saline also caused muscle necrosis, albeit to a lesser extent than did the anesthetic combinations, indicating that both the administration procedure and the pH of the preparation contribute to local tissue damage.

When assessing the surgical tolerance of rodents, the pedal reflex is considered the most sensitive and reliable parameter.[5,10] In our current study, both anesthetic combinations led to comparable levels of anesthesia and time to loss of reflexes. Although there was no significant differences between groups in the loss of righting, pedal, and ear pinch reflexes, rats in the KD group lost palpebral reflexes faster than did those in the KX group. In the KX group, pedal reflex, which is indicative of a surgical plane of anesthesia, was retained in 2 of 11 (18%) animals throughout the 30-min anesthetic period. Previous studies in mice have identified similar variability in the response to KX anesthesia when used alone or in combination with 2 analgesic agents.[5,10] Furthermore, previous reports have described similar findings of variability to KX anesthesia after intraperitoneal administration to rodents, resulting from injection failure (reported to be as low as 1% to 2%) due to inadvertent injection into muscle, subcutaneous tissue, intestine, and other organs.[21,22] In the current study, a single experienced investigator administered all injections in an attempt to reduce variability that could occur between administrators. Alternatively, the variability in responses to KX rodent anesthesia across subjects has been attributed to strain and stock differences;[10,22,37] however, we were unable to determine the cause of the anesthetic failure in our 2 rats.

Both dexmedetomidine and xylazine may cause bradycardia and respiratory depression.[12,28] Previous studies have shown dose-dependent variability in the degree of cardiovascular and respiratory alterations during anesthesia with either KX or KD combinations.[34] Other authors[17] reported significant cardiovascular and respiratory depression in animals anesthetized with KX. However, in our study KX led to increases in heart rate, which most likely are the result of ketamine's cardiostimulatory effects.[30,33] In addition, KX administration led to a brief reduction in respiratory rate, which returned to baseline after administration of atipamezole. KD administration led to bradycardia, respiratory depression, and hypoxemia. The administration of anesthetic combinations containing dexmedetomidine has been shown to lead to reductions in central adrenergic outflow, thus eliminating ketamine's cardiostimulatory effects and resulting in a dexmedetomidine-induced bradycardia.[8,23,30] Our results indicate that both anesthetics cause significant reductions in multiple physiologic parameters that we measured, therefore warranting careful anesthetic monitoring during procedures.

Atipamezole is a highly selective and specific $\alpha_2$–adrenoreceptor antagonist that inhibits and reverses the actions of xylazine and dexmedetomidine.[1,28] We found that subcutaneous administration of atipamezole after 30 min of anesthesia in the KD group led to rapid return of physiologic parameters to baseline levels; however, recovery from anesthesia was significantly delayed.[14] Our findings are in agreement with previous studies that describe the early administration of atipamezole subcutaneously (earlier than 40 min after anesthetic induction) in rodents anesthetized with KM or KD resulted in a prolonged

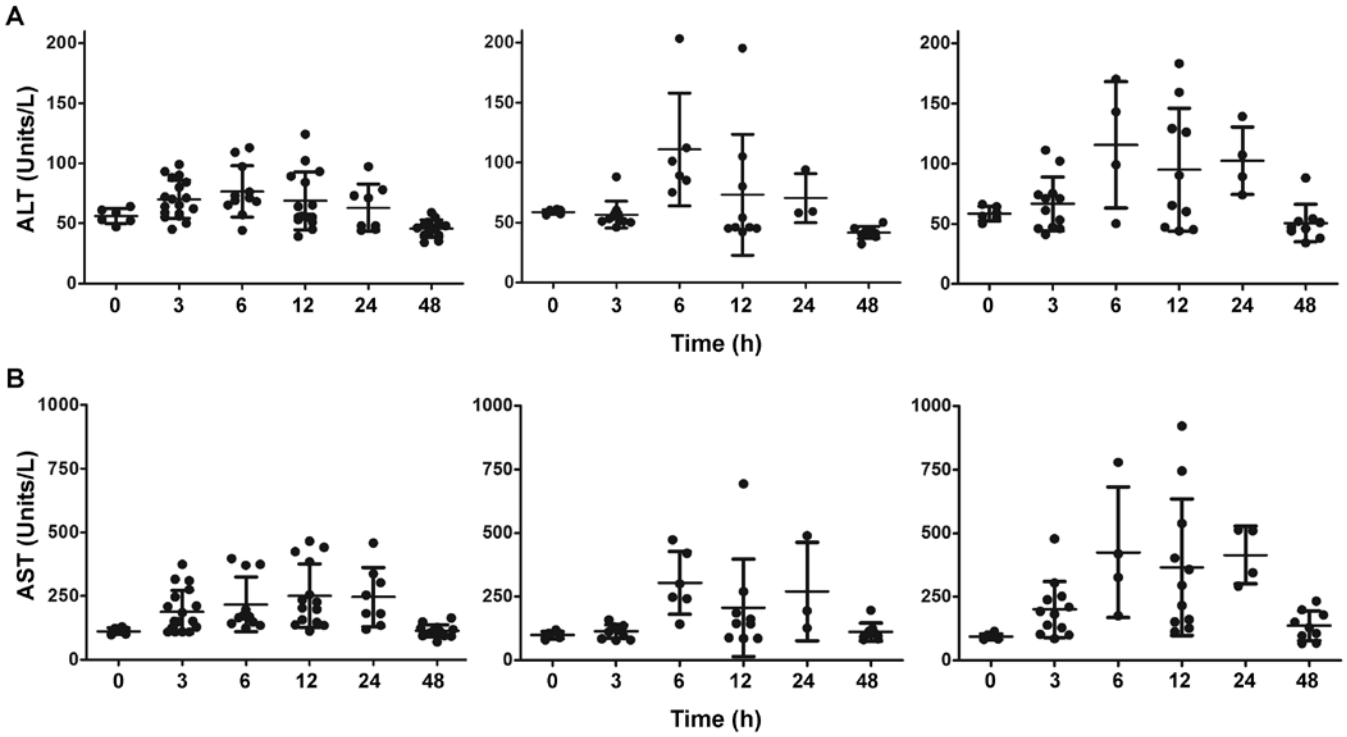


**Figure 6.** Effect of intraperitoneal administration of saline (left), KD (middle), and KX (right) on serum (A) ALT and (B) AST levels.

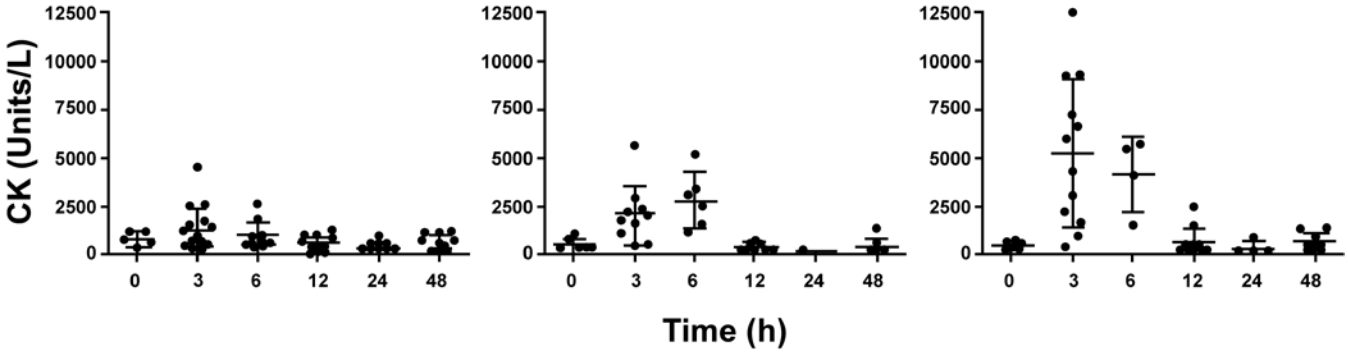


**Figure 7.** Effect of intraperitoneal administration of saline (left), KD (middle), and KX (right) on serum CK levels.

anesthetic recovery.[6] The authors[6] concluded that the prolonged recovery after the administration of the reversal agent was most likely due to ketamine's predominate dissociative effects after antagonism of dexmedetomidine. In light of these findings, additional work is required to determine the optimal time at which to administer atipamezole to achieve rapid reversal in rats anesthetized with KD.

The 2 anesthetic combinations we tested caused transient increases in serum CK, ALT and AST concentrations. These increases may compromise the results of studies where these parameters are measured shortly after anesthesia. Of note, the nature and severity of the muscle-associated findings at the intraperitoneal injection site are similar to those reported by others for ketamine combinations administered intramuscularly,[20,36] suggesting that back-flow of the anesthetics may have contributed to these lesions.[39]

The current study identified marginal increases of serum AST and ALT concentrations in rats given KD or KX intraperitoneally. Our rationale for the evaluation of these parameters was concerns about the potential peritoneal inflammation due to intraperitoneal administration of anesthetic combinations with low pH. However, serum ALT and AST concentrations increases were identified after intramuscular anesthetic administration in previous studies[18,35,44] and in individual rats given saline intraperitoneally in our current study. In the absence of histomorphologic evidence of peritoneal inflammation and liver damage, the increases of serum ALT and AST concentrations that we observed may reflect a systemic effect of the anesthetic combinations rather than peritoneal inflammation or liver damage due to intraperitoneal administration of a low pH anesthetic combination. Alternatively, the increases of serum ALT and AST concentrations in the KX, KD, and saline groups may have been due to the resulting muscle damage after injection or anesthetic administration.[26,31] Of note, similar increases in serum ALT and AST concentrations commonly occur in toxicology studies in the absence of a histomorphologic correlate.[9]

Another objective of our work was to assess the effects of intraperitoneal anesthetic administration on serum CK concentrations in rats. Several studies have evaluated the ef-

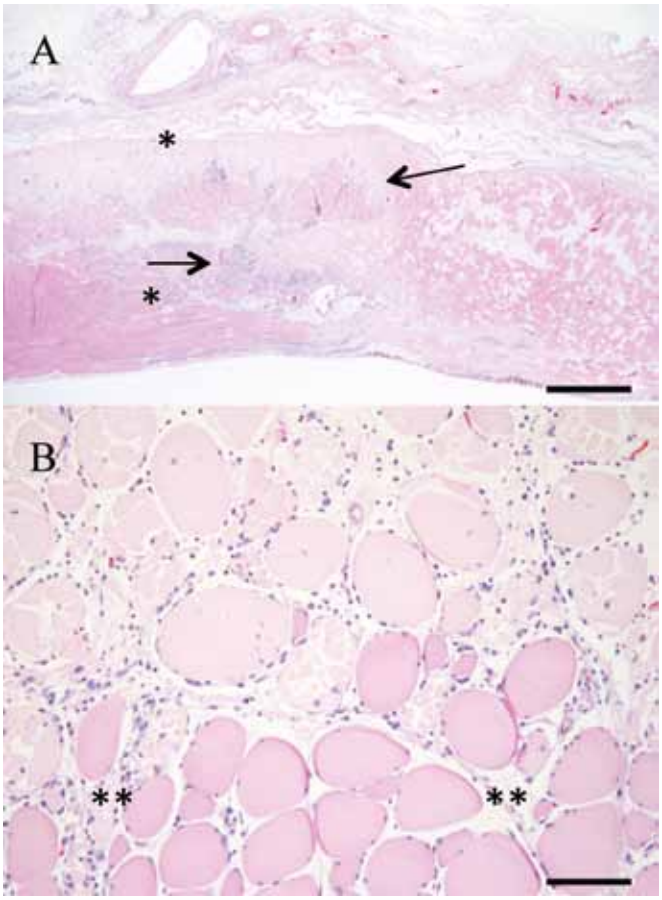


**Figure 8.** Intraperitoneal administration of KX resulted in (A) acute muscle necrosis (*) extending from the subcutis (top of the photomicrograph) through the full thickness of the abdominal wall. The area of necrosis is surrounded by a mild neutrophilic and histiocytic response (arrows). Bar, 1.6 mm. (B) There was a sharp transition from the areas of muscle necrosis (**) to the areas of viable muscle fibers. Bar, 200 µm. KD, atipemazole, and saline caused changes of similar nature but of lesser severity.

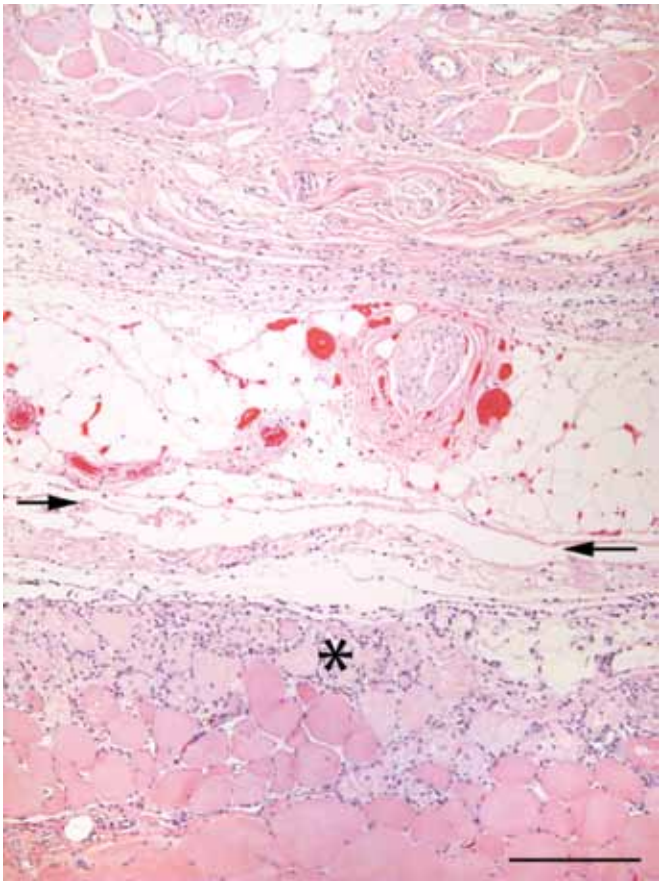

**Figure 9.** Representative photomicrographs of subcutaneous inflammation in rats receiving atipamezole subcutaneously. Subcutaneous administration of atipamezole resulted in subcutis (top of photomicrograph) necrosis and inflammation (*). Hematoxylin and eosin stain; scale bars, 500 µm.

fects of intramuscular anesthetic administration on serum CK levels.[15,24,29] In the current study, serum CK levels were higher in the KX group than in the KD group at 3 h after anesthetic administration. These data showed a clear association between increases in serum CK concentration with increasing severity in muscle necrosis. Serum CK levels returned to baseline levels at 48 h after the initial injection in all groups. Similar transient elevations of serum CK levels occurred in guinea pigs after intramuscular KX.[15]

In conclusion, our current data showed that KX and KD led to comparable levels of anesthesia sufficient for a 30-min surgical procedure. However, anesthesia with KD led to bradycardia, respiratory depression, and subsequent hypoxemia, which were rapidly reversed after subcutaneous administration of atipamezole. Both KD and KX were associated with poor local tolerance characterized by the expression of momentary pain and discomfort on administration, localized tissue damage consisting predominantly of muscle necrosis, and a transient increase in serum ALT, AST, and CK levels. The current study provides evidence that the intraperitoneal administration of KD has better local tolerance than that of KX yet provides anesthesia of similar quality and depth.

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