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Original Research

Ketamine Tolerance in Sprague–Dawley Rats after Chronic Administration of Ketamine, Morphine, or Cocaine

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Ketamine is one of the most commonly used anesthetics in human and veterinary medicine, but its clinical effectiveness is often compromised due to tolerance to its anesthetic effects. Although ketamine tolerance has been demonstrated in a number of behavioral measures, no published work has investigated tolerance to ketamine's anesthetic effects other than duration of anesthesia. In addition, a reported practice in anesthesiology is to alter anesthetic doses for procedures when the patient has a history of drug abuse. Empirically investigating the effects of administration of a drug of abuse on ketamine's potency and efficacy to produce anesthesia could help in the creation of anesthetic plans that maximize safety for both clinicians and patients. The goal of the current study was to test the effects of repeated administration of ketamine, morphine, or cocaine on ketamine's ability to produce anesthesia. In 2 studies, male Sprague–Dawley rats received daily injections of ketamine (32 or 100 mg/kg IP), morphine (3.2 or 5.6 mg/kg IP), or cocaine (3.2 or 10 mg/kg IP) for 14 consecutive days and then were tested on day 15 for ketamine-induced anesthesia by using a cumulative-dosing procedure (32 to 320 mg/kg IP). Chronic treatment with either ketamine or morphine—but not cocaine—produced tolerance to ketamine's anesthetic effects in a dose-dependent manner. These results suggest that ketamine's clinical effectiveness as an anesthetic will vary as a function of its history of use. Furthermore, given that chronic morphine administration produced tolerance to ketamine's anesthetic effects, various pain medications may reduce ketamine's effectiveness for anesthesia.

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Since its introduction in 1964, ketamine has been widely used as an anesthetic in both human and veterinary medicine. Ketamine, a noncompetitive NMDA antagonist with a wide margin of safety, is an FDA-approved drug for use in humans, NHP, and cats.[29] Ketamine is approved for restraint or as the sole anesthetic agent for brief procedures that do not require muscle relaxation, such as diagnostics and physical exams, and this drug is commonly used as a sedative in emergency and pediatric procedures.[26,39] Ketamine's short duration of action makes it an ideal choice for veterinarians as an anesthetic and sedative for short and noninvasive procedures. However, as with many drugs, a limitation of the clinical use of ketamine is tolerance. As such, ketamine's reliability to produce predictable anesthesia, in terms of chemical restraint, is important for the safety of the veterinarian and the wellbeing of the patient. For the purpose of this paper, ketamine's anesthetic effects refer to its ability to immobilize patients, and not a total loss of muscle tone as seen with surgical anesthesia.

In cases where ketamine is indicated as an anesthetic, patients with a history of chronic ketamine use often receive an increased dose, to compensate for potential tolerance.[21,25] In addition, there have been several reports of children who required increased doses of ketamine after being repeatedly sedated for various procedures, including radiation therapy.[8,23,38] Interestingly, little research has been published regarding tolerance to ketamine's anesthetic effects. Although several studies demonstrate that repeated doses of ketamine can shorten the duration of its anesthetic effects, the effects of chronic ketamine treatment on the drug's ability to produce reliable anesthesia or on the grade of anesthesia (that is, level of anesthetic depth) are not addressed.[7,22,31,35] Given ketamine's clinical use and its rise in recent years as an illicit drug, there is a need to better understand the effects that a history of ketamine administration has on its anesthetic efficacy.[1]

Prior to an anesthetic procedure, human patients are asked to complete a questionnaire that includes pertinent health information, including drug use. Regarding ketamine anesthesia, patients with a history of illicit drug use may receive increased doses.[14,17,34] The rationale for this adjustment appears to be based largely on anecdotal evidence, because no studies have been published that investigate the effects of prior exposure to drugs of abuse on the anesthetic effectiveness of ketamine. In 2016 in the United States, approximately 28.6 million people older than 12 y had used an illicit drug in the past 30 d; approximately 1.4 million people were reported to use hallucinogens (including ketamine), 11.8 million people were misusing opioids, and 1.9 million people were using cocaine.[1] Therefore, there is a clear need to investigate the effects of a history of illicit drug exposure on ketamine's anesthetic effectiveness.

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The goals of this study were 2-fold: to determine 1) whether chronic ketamine administration produces tolerance to its anesthetic effect, and b) whether chronic administration of an opioid or stimulant—2 drug classes that are highly abused—alters ketamine's effectiveness as an anesthetic. To simulate chronic illicit drug use, we administered drugs for 14 consecutive days. After chronic drug administration, the subjects received intraperitoneal injections of ketamine in a cumulative-dosing procedure, and anesthetic depth was evaluated. We hypothesized that all of the test drugs would reduce ketamine's anesthetic potency or efficacy in a dose-dependent manner (that is, produce tolerance).[7,10,14,17]

Materials and Methods

Animals. This study was conducted at an AAALAC-accredited facility according to an IACUC-approved protocol and in compliance with the 8th edition of *Guide for the Care and Use of Laboratory Animals*.[20] Male Sprague–Dawley rats (n = 64; weight, 310 ± 32 g) were obtained from Envigo (Fredrick, MD). The housing environment was maintained at 22 ± 2 °C, with a relative humidity of 30% to 70% on a reverse 12:12-h dark:light cycle (lights on, 1900 CST). Rats were housed 2 per standard polypropylene shoebox cage (10.5 × 19 × 8 in., Ancare, Bellmore, NY) on wood chip bedding and had unrestricted access to a commercial rodent diet (Teklad 8640, Envigo) and water. Paper twists and a wooden chew block were supplied for each cage for additional enrichment. Colony health was evaluated every 4 mo through sentinel exposure to dirty bedding. All sentinels were seronegative for *Mycoplasma pulmonis, Pneumocystics carinii*, rat parvoviruses, rat coronaviruses, rat minute virus, Kilham rat virus, H1 virus, Sendai virus, pneumonia virus of mice, reovirus 3, lymphocytic choriomeningitis virus, and Sendai virus. PCR testing was negative for fur mites and pinworms.

Rats were randomly divided into 3 pretreatment groups for chronic exposure to ketamine, morphine, or cocaine. Each pretreatment group comprised 3 subgroups: a saline control, a low-dose pretreatment group, and a high-dose pretreatment group.

Drugs. Cocaine HCl (National Institute on Drug Abuse, Bethesda, MD) and morphine sulfate (Sigma-Aldrich, St Louis, MO) were administered in a solution of 0.9% NaCl. Pharmaceutical grade ketamine HCl (100 mg/mL; Henry Schein Animal Health, Dublin, OH) was diluted in sterile 0.9% NaCl, except for the 320-mg/kg cumulative dose, which was administered directly from the undiluted pharmaceutical stock at a volume of 1.4 mL/kg. All doses are expressed as the salt.

Chronic ketamine administration *Pretreatment*. Rats in the ketamine pretreatment group were divided into 3 chronic-pretreatment groups (n = 8): low-dose ketamine pretreatments (32 mg/kg) to represent a subanesthetic dose, high-dose ketamine pretreatments (100 mg/kg) to represent a typical anesthetic dose, and a saline control group.[16] After arriving at the facility, rats were allowed to acclimate to their home environment for 48 h before undergoing a 7-d training period in which they were habituated to being handled and restrained in the location where pretreatments and the anesthetic test was to be performed. After the training period, rats were injected IP with their respective pretreatment solutions at a volume of 1 mL/kg for 14 consecutive days. A 14-d pretreatment period was chosen based on previous studies in which morphine and cocaine were administered to produce behaviorally-relevant changes. This period was also used for ketamine so that all studies had comparable handling and treatment duration parameters. Pretreatments were performed at approximately 1200 CST every day in the same location by 4 people. All rats were scored for level of sedation during the pretreatment period (see details on sedation metric below).

***Anesthetic test*.** After the final pretreatment dose, each rat was tested on day 15 for ketamine-induced anesthesia. Testing was performed at approximately 1200 CST for each group, in the same location and under identical conditions as the pretreatments had been administered.

Rats first received intraperitoneal injections of saline and were placed in a clean cage without bedding. After 5 min, rats received cumulative doses of ketamine every 5 min at the amounts required to render a cumulative dose–response series that increased in quarter-log intervals along a range of 32 to 320 mg/kg (for example, after receiving 32 mg/kg, a rat was given an additional 24 mg/kg to achieve a cumulative dose of 56 mg/kg). Cumulative doses of 32, 56, 100, 180, and 320 mg/kg were administered at 5, 10, 15, 20, and 25 min, respectively. All injections were administered in volumes of 1 mL/kg, except for the cumulative 320-mg/kg dose, which was provided as a 140-mg/kg dose in a volume of 1.4 mL/kg. Anesthetic depth was monitored continuously after the initial saline injection. The dose required to reach each level of anesthetic depth was recorded for all rats. The scoring system (Figure 1) was developed on the basis of current veterinary metrics to measure sedation in rats.[3,4,11,27,37,41] Typically, rats do not reach surgical levels of anesthesia when ketamine is administered as a sole agent, and they typically receive a ketamine-containing cocktail with other agents (for example, xylazine) to reach an adequate plane of anesthesia.[16,37,41] For purposes of this study, we chose to administer ketamine only, because xylazine might affect tolerance through mechanisms not produced by ketamine and because providing ketamine as a sole anesthetic is more typical for sedation in a clinical setting. Therefore, we chose presurgical anesthesia (plane III), in which rats show loss of the righting reflex, as the target level for full effect in our study.

Supplemental heat and eye lubrication were applied to each rat that lost consciousness. Rats were monitored until they were fully recovered and thus able to ambulate in the cage without any signs of ataxia. After recovery, rats were euthanized on the test day through CO_2 overdose and creation of a bilateral pneumothorax. Gross necropsies were performed on those rats that died during anesthetic testing.

Chronic administration of morphine and cocaine *Pretreatments*. The administration of morphine and cocaine during the chronic pretreatment period produced 5 pretreatment groups (n = 8 each): low-dose morphine (1.8 mg/kg), high-dose morphine (5.6 mg/kg), low-dose cocaine (3.2 mg/kg), high-dose cocaine (10 mg/kg), and a saline control group. The doses and administration routes of morphine and cocaine were chosen on the basis of conditioned place-preference studies, an assay commonly used to measure the abuse-related effects of drugs, with the goal of including a nonrewarding dose and a fully-rewarding dose of each drug.[9,18,19,24,36,42] That is, in terms of producing abuse-related effects, the doses of morphine and cocaine were functionally matched by including ineffective and effective doses for each drug that were adjacent to one another in their respective dose–response determinations.

***Anesthetic test*.** The day after the final pretreatment with morphine or cocaine, each rat was tested for ketamine-induced anesthesia identically to rats pretreated with ketamine.

Data analysis. For each pretreatment group, the percentage of rats that reached plane III during the anesthetic test was plotted as a function of ketamine dose. The dose–response curves for the 3 groups in the ketamine pretreatment experiment and the 5 groups testing pretreatment with morphine or cocaine were

Anesthetic plane	Description
Plane I: no effect	No anesthetic effect on the animal; rat is behaving normally
Plane II: excitement phase	Excitement, salivation, lacrimation, urination, and defecation. Righting reflex is intact. Rat begins to become ataxic and agitated and may start circling
Plane III: presurgical anesthesia	Loss of righting reflex, loss of consciousness, exaggerated reflexes, purposeless muscular movement

Figure 1. Measures of sedation.

compared by using log-rank tests ($\alpha = 0.05$). Posthoc analyses comparing the saline group to every other group in each experiment were conducted by using log-rank tests with Bonferroni correction to control for increases in familywise error rate.

Mean latency to recovery after from administration of the last ketamine dose delivered during anesthetic testing (cumulative 320 mg/kg IP) to recovery was plotted for each group in both pretreatment experiments. Latency to recovery was compared among the 3 groups in the first experiment and among the 5 groups in the second was conducted by using one-way ANOVA. Within each experiment, Dunnett multiple-comparisons tests were conducted to compare the saline pretreatment group with every other group.

Results

Ketamine. The dose–response curves differed significantly ($X^2_2 = 6.07$, $P < 0.05$) between ketamine pretreatment groups (Figure 2). Posthoc comparisons of dose–response curves detected a significant difference only between the saline and high-dose ketamine groups ($P = 0.0093$). That is, rats that received the high dose of ketamine during pretreatment required significantly ($P < 0.05$) higher doses of ketamine to reach plane III anesthesia than did other groups during anesthetic testing, indicating tolerance to the anesthetic effects of ketamine.

The latency to recovery after administration of the cumulative 320-mg/kg dose of ketamine differed significantly ($F_{2,18} = 10.24$, $P < 0.05$) among pretreatment groups (Figure 2). Dunnett multiple-comparison tests detected significant differences in recovery time between the saline group and both the low-dose and high-dose ketamine pretreatment groups ($P < 0.05$ for both comparisons). That is, rats that received either the low or high dose of ketamine during chronic pretreatment required significantly less time to recover from a cumulative 320-mg/kg IP dose of ketamine than did the saline controls during anesthetic testing.

Morphine and cocaine. Dose–response curves to morphine or cocaine were significantly ($X^2_4 = 12.35$, $P < 0.05$) different between pretreatment groups (Figure 3). Posthoc comparisons of dose–response curves detected a significant ($P = 0.0028$) difference between the saline and high-dose morphine groups only. That is, rats that received high-dose morphine during pretreatment required significantly higher doses of ketamine to reach plane III anesthesia than the saline control group, indicating cross-tolerance to the anesthetic effects of ketamine after chronic high-dose morphine pretreatment.

The latency to recovery after administration of the cumulative 320-mg/kg dose of ketamine did not differ among morphine or cocaine pretreatment groups. Therefore, a history of pretreatment with cocaine or morphine did not affect the recovery time after the administration of a cumulative 320-mg/kg IP dose of ketamine during anesthetic testing.

During anesthetic testing, 4 rats died unexpectedly: 2 rats from the low-dose ketamine pretreatment group, one from the high-dose ketamine pretreatment group, and one from the high-dose cocaine pretreatment group. Each rat had reached plane III anesthesia prior to the dose that led to death. Gross necropsy performed by a veterinarian revealed no gross abnormalities in the rats in the high and low ketamine pretreatment groups other than increased porphyrin staining. An enlarged liver was noted in the rat from the high-dose cocaine pretreatment group. Other findings of the necropsies were unremarkable. Gross necropsy was inconclusive for determining the cause of death, and histopathology was not performed.

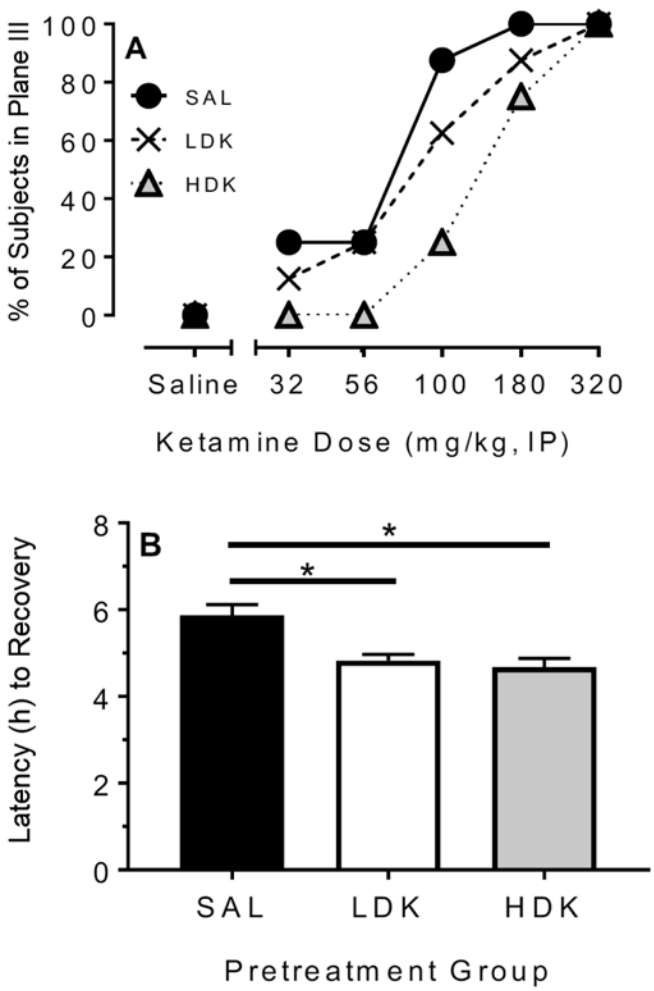

Figure 2. (A) Percentage of subjects in plane III anesthesia as a function of the cumulative ketamine dose. (B) Latency (h) to recovery (mean ± SEM after administration of the last dose in the anesthetic test (cumulative, 320 mg/kg IP) across pretreatment groups. *, $P < 0.05$ compared with value for saline control group. HDK, high-dose ketamine (100 mg/kg); LDK, low-dose ketamine (32 mg/kg); SAL, saline.

Discussion

The results of our study support our hypothesis that rats that received chronic pretreatment with ketamine or an opioid required increased doses of ketamine to reach the target anesthetic plane but disproved our hypothesis that rats receiving cocaine pretreatment would need additional ketamine to reach the same plane of anesthesia as those without pretreatment. These results may be relevant to the formation of ketamine-containing anesthetic plans for human patients, in particular those who have recently used opioids. Our findings

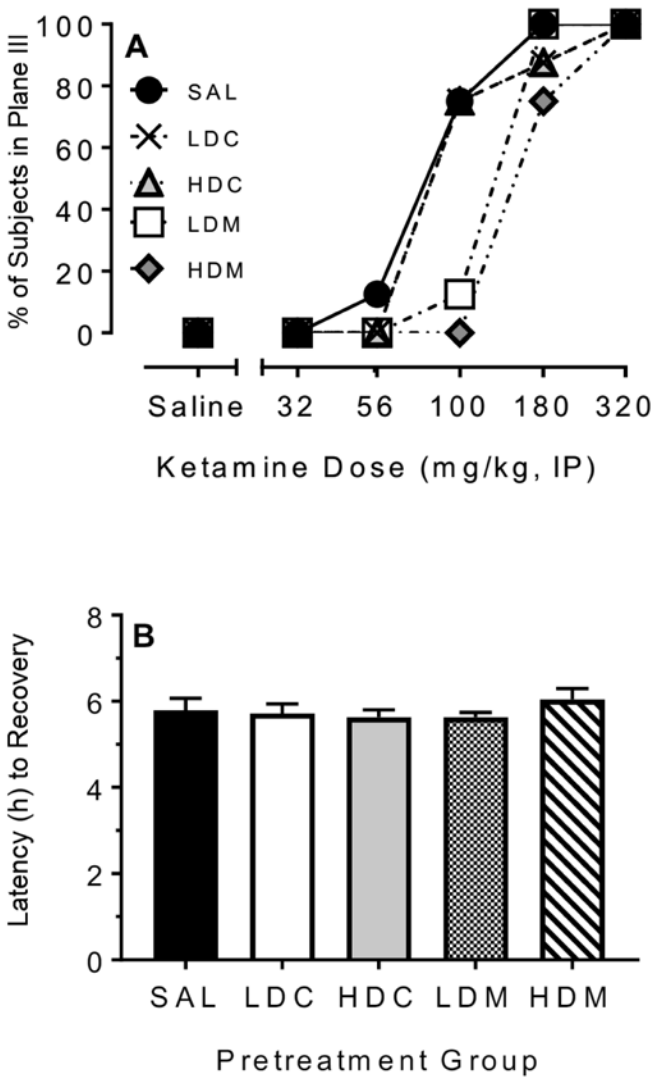

Figure 3. (A) Percentage of subjects in plane III anesthesia as a function of the cumulative ketamine dose. (B) Latency (h) to recovery (mean ± SEM after administration of the last dose in the anesthetic test (cumulative, 320 mg/kg IP) across pretreatment groups. HDC, high-dose cocaine (10 mg/kg); HDM, high-dose morphine (5.6 mg/kg); LDC, low-dose cocaine (3.2 mg/kg); LDM, low-dose morphine (1.8 mg/kg); SAL, saline.

that chronic ketamine administration produced tolerance to its anesthetic effects suggests that observations of tolerance-like effects in laboratory and clinical practice may be due, in part, to a history of ketamine use. Rats pretreated with high doses of ketamine not only needed significantly more ketamine to reach plane III but also had a shorter duration of anesthesia, which is consistent with previous reports.[7,10,22] The shorter anesthetic duration in the ketamine-pretreated rats may be explained by the induction of liver enzymes that metabolize ketamine.[2,7,10,22] In addition, ketamine can cause changes in the brain, such as neuroplasticity and neuropoptosis in neonatal rhesus macaques, which may further explain the tolerance we observed.[6,33] The reliability of ketamine as an anesthetic is important for researchers and veterinarians that specialize in laboratory animal medicine, because it is commonly the drug of choice for short procedures, such as physical examinations. Our current results might explain why subsequent sedations with ketamine can be less effective and shorter duration and suggest that it may be beneficial to increase the dose of successive sedations or switch anesthetics in animals undergoing frequent sedations.[7,10,22] What remains to be determined is how long tolerance to ketamine's anesthetic effects persists after chronic administration has ceased and the effects of intermittent ketamine sedation in relation to tolerance. It is not uncommon to sedate NHP intermittently to perform physical examinations, tuberculin testing, or for health reasons. A study that focuses on intermittent rather than daily administration would be helpful to determine whether this type of dosing also produces tolerance to ketamine's anesthetic effects.

In regard to cross-tolerance, only rats in the high-dose morphine pretreatment groups demonstrated cross-tolerance to ketamine's anesthetic effects. Surprisingly, rats in the cocaine pretreatment groups did not need more ketamine to reach plane III than the saline control group. Although the mechanisms of tolerance and cross-tolerance were outside the scope of this study, cross-tolerance between ketamine and morphine may partially be explained by ketamine's action as a partial agonist at μ opioid receptors.[26] The cross-tolerance demonstrated between opioids and ketamine suggests that animals on protocols involving chronic opioid administration may require increased doses of ketamine or different anesthetic drugs. Given our findings, patients with cancer pain who are managed with opioid medication may become tolerant of ketamine-induced anesthesia, thus affecting anesthetic stability during radiologic procedures.[8,23,38] Although not assessed in humans, the results of our current study do not indicate a need to adjust ketamine doses after chronic stimulant use. However, clinicians may want to avoid the combination of these drugs, in light of potentially adverse cardiovascular effects.[15]

Ketamine has seen growing popularity as an antidepressant in patients who are resistant to traditional treatment.[12,15,16,40,43] There are reports of animals becoming tolerant to the antidepressive effects of ketamine during repeated administrations, and ketamine's effectiveness as an antidepressant has been reported to be transient in humans.[5,30] Alternatively, subanesthetic doses of ketamine are commonly used to create an experimental model of schizophrenia.[32] These doses of ketamine have been demonstrated in the past to create a behavioral tolerance, but not to ketamine as an anesthetic.[13,28] Given the results of the current study, researchers and veterinary clinicians alike may need to consider adjusting their anesthetic doses of ketamine while working with animals dosed with ketamine for these nontraditional purposes. In addition, it appears there is a need to investigate the effects of tolerance that these subanesthetic doses of ketamine produce in people who use ketamine as an adjuvant to traditional therapies. However, it should be noted that the low-dose ketamine pretreatment group showed a significant reduction in time to recovery only and not significant increase in ketamine dose to induce anesthesia.

Much research remains to be done on the topics of ketamine tolerance and cross-tolerance to ketamine, but our findings provide crucial information for future investigations. These results show that tolerance that develops with daily ketamine use, but a study correlating tolerance to intermittent drug use would more closely mimic binge drug users and intermittent sedation for treatments in pediatric, laboratory, and veterinary medicine. Alternatively, determining ketamine tolerance to its use in an anesthetic cocktail, such as a ketamine–xylazine combination, would be beneficial for laboratory animal veterinarians. Although research exists to support tolerance to ketamine's behavioral effects, future implications may include determining doses or withdrawal periods to mitigate reverse this tolerance.[13]

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