

Use of the anesthetic combination of tiletamine, zolazepam, ketamine, and xylazine for neutering feral cats

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Objective—To evaluate the use of the anesthetic combination tiletamine, zolazepam, ketamine, and xylazine (TKX) for anesthesia of feral cats at large-scale neutering clinics.

Design—Original study.

Animals—7,502 feral cats.

Procedure—Cats were trapped by their caretakers for a feral cat neutering program from July 1996 to August 2000. The anesthetic combination TKX was injected IM into cats while they remained in their traps. Each milliliter of TKX contained 50 mg of tiletamine, 50 mg of zolazepam, 80 mg of ketamine, and 20 mg of xylazine. Females were spayed by veterinarians, whereas males were castrated by veterinarians or veterinary students. Yohimbine (0.5 mg, IV) was administered at the end of the procedure. Logs were kept of the individual drug doses, signalment of the cats, and any complications encountered. These data were analyzed retrospectively (1996 to 1999) and prospectively (2000).

Results—Of the 5,766 cats for which dosing records were complete, 4,584 (79.5%) received a single dose of TKX. The mean initial dose of TKX was 0.24 ± 0.04 ml/cat, and the total mean dose of TKX was 0.27 ± 0.09 ml. Overall mortality rate was 0.35% (26/7,502) cats, and the death rate attributable solely to potential anesthetic deaths was 0.23% (17/7,502) cats.

Conclusions and Clinical Relevance—The use of TKX for large-scale feral cat neutering clinics has several benefits. The TKX combination is inexpensive, provides predictable results, can be administered quickly and easily in a small volume, and is associated with a low mortality rate in feral cats. (*J Am Vet Med Assoc* 2002; 220:1491–1495)

Feral cats are domesticated cats that have reverted to a wild state. Unsocialized feral cats avoid human contact and can be tamed only with great effort. They are refractory to human handling and for safety reasons should be regarded as wild animals. They are present worldwide and constitute a large portion of cats euthanatized at animal shelters. In the United States alone, the feral cat population is estimated to be as high as 60 million and may exceed the population of owned

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cats.^{1a} Attempts to reduce this overpopulation by trap and removal methods have been largely unsuccessful, as the cats remaining in the colonies continue to breed, thereby filling the void left by those that were removed.² Feral cat neutering through trap-neuter-return (TNR; castration or spay) programs is a non-lethal alternative for feral cat population control. In these programs, feral cats are trapped for neutering and then returned to their colonies. Trap-neuter-return programs are an increasingly popular alternative for controlling feral cat overpopulation. Trap-neuter-return as a means to control feral cat overpopulation is currently endorsed by the American Veterinary Medical Association.^b

Today, veterinarians are increasingly called on to participate in feral cat neutering either on an individual cat basis or in organized large-scale settings. Large-scale feral cat clinics are designed to spay and castrate a large number of cats at a time, sometimes in temporary facilities, and often with volunteers. The anesthetic protocol is, therefore, an essential component if these clinics are to operate effectively. An ideal anesthetic agent for feral cats would have a wide margin of safety, provide rapid and predictable surgical anesthesia, provide postoperative analgesia, be reversible, be inexpensive, and be simple to administer to trapped cats. The combination of tiletamine, zolazepam, ketamine, and xylazine (TKX) meets many of these requirements and has been used by several large-scale feral cat neutering programs.^{c,d} Use of TKX has been reported to be a suitable anesthetic for castration and onychectomy of pet cats.³ However, to our knowledge, the use of TKX in feral cats (for which there is a unique set of challenges for the safety of both the cats and clinic workers) has not been reported. The purpose of the study reported here was to determine whether use of TKX adequately met the anesthetic requirements for feral cats undergoing neutering in a large-scale clinic.

Materials and Methods

Cats—Feral cats were trapped by caretakers in the Raleigh, NC (July 1996 to August 2000) and Gainesville, Fla (July 1998 to August 2000) regions. These cats were admitted to monthly feral cat neutering clinics at the Colleges of Veterinary Medicine at North Carolina State University and the University of Florida.^d The number of cats neutered during each period ranged from 60 to 208. The clinics were staffed by volunteers and were offered at no fee to the public. Cats were trapped by caretakers and brought into the clinic in wire traps or plastic crates. On arrival at the clinics, cats were assigned an identification number.

Anesthetic protocol—A combination of TKX was used to induce anesthesia. One bottle of tiletamine-zolazepam^c (con-

sisting of equal parts of tiletamine and zolazepam) in powder form was reconstituted with 4 ml of ketamine^f (100 mg/ml) and 1 ml of 10% xylazine^g (100 mg/ml) in place of the water that is recommended by the manufacturers. Thus, each milliliter of reconstituted TKX contained 50 mg of tiletamine, 50 mg of zolazepam, 80 mg of ketamine, and 20 mg of xylazine. On the basis of a subset of 194 cats that were weighed, the mean weight of the cats was 3.04 ± 0.8 kg (6.69 ± 1.76 lb). The standard dose for an adult cat was 0.25 ml of the anesthetic combination solution. This amount was adjusted according to the estimated size of the cat. When necessary, additional doses of TKX were administered to achieve sufficient anesthetic depth. Supplemental doses were generally 0.05 to 0.25 ml and estimated on the basis of the size of the cat, stage of the surgical procedure, and estimated plane of anesthesia. The drug was administered IM into the lumbar or thigh muscles through the wire mesh of a humane trap or crate while the cat remained in the trap.

Clinic procedures—For safety reasons, cats were not removed from the traps until they were unconscious. Thus, it was not possible to weigh or examine cats prior to anesthetic administration. An identification tag was placed on each cat on removal from the trap or crate. Cats were then taken to presurgical stations where the tip of the left ear was removed to permanently identify them as neutered. Vaccinations against panleukopenia, rhinotracheitis, calicivirus, FeLV, and rabies were administered, and cats received various medications for internal and external parasites. Female cats were spayed by veterinarians. Males were castrated by veterinarians or veterinary students, with the exception of cryptorchid males, which were castrated by veterinarians. Absorbable buried sutures were used to prevent the need for future suture removal. During the course of the surgical procedures, cats were manually monitored for respiratory pattern, heart rate, and mucous membrane color. Following surgery, 0.5 mg of yohimbine^h (2 mg/ml) was administered IV to adult cats, and 0.3 mg was administered to kittens. Cats were replaced in their traps before recovery. Volunteers supervised the recovery with visual monitoring of the cats in their traps for respiration, hemorrhage, and progressive return to consciousness (sternal recumbency). Cats were returned to their caretakers later the same day. Necropsies were performed on any cat that died during or after the procedure to determine, if possible, the cause of death.

Data collection—A log was kept with each cat's identification number, initial drug dose given, and any additional doses required. A second log was kept to record each cat's sex, details regarding its reproductive status, body condition, and any surgical or anesthetic complications. These records were collected and analyzed retrospectively (1996 to 1999) and prospectively (2000). From these records, a profile of the cats admitted to the clinic was created, mortality rates were calculated, and anesthetic dosing patterns were determined. As the purpose of the study was to evaluate the use of TKX in a typical high-volume feral cat clinic, no attempt was made to alter the routine clinical procedures already in place by collecting additional data or instituting more intensive monitoring procedures. Certain categories of surgery, such as spaying pregnant females, confirmation of previous ovariectomy, and castration of cryptorchid males, were often of longer duration and more invasive than routine surgeries. Therefore, females were assigned to 1 of 3 groups according to whether they were pregnant, previously spayed, or nonpregnant and sexually intact (routine ovariectomy). Males were also assigned to 1 of 3 categories according to whether they were cryptorchid, previously castrated, or sexually intact (routine castration). Volume of first TKX injection, total volume of all injections, and total number of injections were recorded for each cat.

Statistical analyses—Mean and median TKX volume

and number of injections administered were compared for all females versus all males. In addition, the various categories of females were compared with each other, and categories of males were compared with each other. A comparison was also made between total number of surviving cats and cats that died. Wilcoxon rank sum tests were performed to test shifts in location of 2 independent samples. The Bonferroni correction was applied by dividing the overall significance level of 0.05 by the total number of significance tests performed (16) for each data point (this was an attempt to maintain the overall false-positive rate near 5% [$\alpha = 0.05$] when a large number of comparisons is made). Therefore, each test performed was compared to a significance level of $\alpha = 0.003$ ($0.05/16$). Each test was considered significant at values of $P < 0.003$.

Results

From July 1996 to August 2000, 7,502 cats were admitted in Raleigh, NC ($n = 4,276$) and Gainesville, Fla (3,226). Overall, 4,427 (59%) of the cats were female, and 3,038 (40.5%) were male; sex was not recorded for 37 (0.5%) cats. Of the females, 792 (17.9%) were pregnant, and 65 (1.5%) were previously spayed (either a scar from a previous spay was evident during surgical preparation or previous ovariectomy was surgically verified). Of the males, 35 (1.2%) were cryptorchid, and 46 (1.5%) were previously castrated. Complete records existed for 5,766 (76.9%) of the cats, because only partial records were available for the clinics operating from July 1996 to December 1997.

Mean initial dose of TKX was 0.24 ± 0.04 ml/cat, and total mean dose of TKX, including supplemental doses, was 0.27 ± 0.09 ml. Overall, 4,584 (79.5%) cats received a single dose of TKX, 969 (16.8%) received 2 doses, 180 (3.1%) received 3 doses, 30 (0.5%) received 4 doses, and 3 (0.1%) received 5 doses of the anesthetic combination.

Of the pregnant females, 482 (76.6%) received only 1 dose of TKX; of the previously spayed females, 36 (72%) received 1 dose; and of the routinely spayed females, 2,070 (78.1%) received 1 dose. The mean initial volume of TKX \pm SD administered to all females ($n = 3,334$) was 0.24 ± 0.04 ml, to routinely spayed females (2,655) was 0.24 ± 0.05 ml, to pregnant females (628) was 0.25 ± 0.03 ml, and to previously spayed females (51) was 0.25 ± 0.03 ml. The mean number of doses \pm SD administered to all females was 1.27 ± 0.56 doses, to routinely spayed females was 1.27 ± 0.56 doses, to pregnant females was 1.27 ± 0.53 doses, and to previously spayed females was 1.39 ± 0.7 doses. The mean total volume \pm SD administered to all females was 0.28 ± 0.09 ml, to routinely spayed females was 0.27 ± 0.09 ml, to pregnant females was 0.29 ± 0.08 ml, and to previously spayed females was 0.30 ± 0.11 ml. The median number of doses administered to all females regardless of grouping was 1 dose, and the median total volume was 0.25 ml.

Of the cryptorchid males, 20 (66.7%) received 1 dose of TKX; of the previously castrated males, 30 (83.3%) received 1 dose; and of the routinely castrated males, 1,935 (82.1%) received 1 dose. The mean initial volume of TKX \pm SD administered to all males ($n = 2,402$) was 0.24 ± 0.04 ml, to routinely castrated males (2,334) was 0.24 ± 0.04 ml, to cryptorchid males (31) was 0.25 ± 0.02 ml, and to previously neutered males

(37) was 0.25 ± 0.02 ml. The mean number of doses \pm SD administered to all males was 1.22 ± 0.5 doses, to routinely castrated males was 1.22 ± 0.5 doses, to cryptorchid males was 1.35 ± 0.55 doses, and to previously neutered males was 1.19 ± 0.46 doses. The mean total volume \pm SD administered to all males was 0.27 ± 0.08 ml, to routinely castrated males was 0.27 ± 0.08 ml, to cryptorchid males was 0.30 ± 0.09 ml, and to previously neutered males was 0.28 ± 0.08 ml. The median number of doses administered to all males regardless of grouping was 1 dose, and the median total volume was 0.25 ml.

Significant differences were not detected between males and females overall in total volume of TKX administered ($P = 0.872$), but females were given significantly ($P < 0.001$) higher numbers of injections. Female cats that were pregnant received a higher mean anesthetic volume than females undergoing routine spays ($P = 0.001$) but not an increased number of injections ($P = 0.383$). There was no significant difference in total anesthetic volume ($P = 0.018$) or number of injections ($P = 0.237$) administered to previously spayed females, compared with routinely spayed females. There were also no significant differences in total anesthetic volume ($P = 0.092$) or number of injections ($P = 0.084$) administered to cryptorchid males, compared with routinely castrated males. Likewise, there were no significant differences in total anesthetic volume ($P = 0.319$) or number of injections ($P = 0.776$) administered to previously castrated males, compared with routinely castrated males.

Of the 7,502 cats in the study, 26 (0.35%) cats died between the administration of the anesthetic and the time of discharge to their caretakers. Necropsies were performed on all cats that died unexpectedly. Physical abnormalities that may have contributed to unexpected perioperative deaths were identified in 9 cases. These abnormalities include upper respiratory disease and anemia ($n = 1$), laryngotracheitis and pneumonia (1), right ventricular dilated cardiomyopathy (1), dirofilariasis (1), aspiration pneumonia (1), diaphragmatic hernia (1), intestinal neoplasia (1), lymphoma (1), and surgical hemorrhage (1). In 17 (0.23%) cats, no considerable abnormalities were identified at necropsy, and the cause of death was therefore attributed primarily to a potential anesthetic complication. Anesthetic records were available for 20 of the cats that died. Cats that died during the course of the clinics received 0.24 ± 0.05 ml of TKX. These cats did not receive a significantly different total dose of anesthesia than the total population ($P = 0.307$) or a significantly different number of injections ($P = 0.503$). Of the 17 cats that died of unknown causes, anesthesia records were available for 11 cats. Eight (72.7%) of these cats received only 1 dose of TKX, and 3 (27.3%) received a single supplemental dose.

Discussion

In cats, TKX has been used for onychectomy and castration.³ The anesthetic combination consists of tiletamine hydrochloride, zolazepam hydrochloride, ketamine, and xylazine. Tiletamine is a dissociative anesthetic that is chemically related to ketamine; it pro-

vides analgesia, immobilization, and dissociative anesthesia with increasing doses.^{4,5} Zolazepam is a benzodiazepine that induces muscle relaxation.⁵ The analgesic effects of tiletamine and zolazepam usually persist after the anesthetic effects have diminished,⁵ and the result is a state of sedation, immobility, and visceral analgesia.

Ketamine is also a rapid-acting, nonnarcotic, nonbarbiturate drug. Similar to tiletamine, ketamine also creates a dissociative anesthetic state. Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist.⁶ It is thought that ketamine can prevent the development of central hyperalgesia by its inhibition of NMDA receptors, which are reported to play an essential role in the development of central pain sensitization.⁷ Several studies^{8,9} have documented these preemptive analgesic effects of ketamine. A specific study¹ on the analgesic effects of ketamine in spayed female cats revealed that ketamine is a weak visceral analgesic. Ketamine was shown to increase the threshold to noxious stimuli in these cats, thus providing visceral analgesia. The preemptive visceral analgesic properties of ketamine confer a benefit to the TKX anesthetic combination by preventing noxious stimuli associated with surgery from upregulating the sensitivity of the CNS.

Xylazine is an α_2 -adrenergic receptor agonist. Xylazine centrally inhibits interneural transmission, inducing muscle relaxation, depression of the CNS, and visceral analgesia.¹⁰ The analgesic effects of xylazine are not dose dependent, lasting only 20 minutes even when xylazine is administered in high doses.¹¹ The effects of xylazine can be reversed with an α_2 -adrenergic receptor antagonist such as yohimbine.¹² Because of the short analgesic effects of xylazine, yohimbine reverses the residual sedative effects produced by xylazine.

The anesthetic combination of TKX is unique, because it consists of 2 dissociative anesthetic agents and 3 agents that provide analgesia. By reconstituting the tiletamine-zolazepam mixture with ketamine and xylazine in place of water, surgical anesthesia can be attained with a small volume. The TKX combination creates a balanced anesthetic by targeting distinct drug receptors in the CNS to reduce the amount of each individual drug required, while simultaneously providing more analgesia and sedation than could be produced by a single drug.³ The use of yohimbine adds an additional benefit to the anesthetic combination, because recovery can be hastened by reversing the residual sedative effects of xylazine.

The feral cat neutering clinics in this report were unique, because up to 200 cats were frequently anesthetized during a 3- to 4-hour period in a single day. These clinics were organized for maximum volume and cost effectiveness in which up to 12 surgeries were performed simultaneously. The large numbers of cats anesthetized at 1 time, limited veterinary personnel, and financial constraints limited the anesthetic monitoring of clinic patients. Although electronic monitoring of patients is valuable and ideal, in some large-scale neutering clinics it is not practical. The American College of Veterinary Anesthesiology (ACVA) has established guidelines for anesthetic monitoring. It is recognized that in some clinic settings, monitoring

with specialized equipment is not feasible. The ACVA suggests that circulation, oxygenation, and ventilation be monitored.¹³ The cats anesthetized during the clinics in this study were monitored by assessment of mucous membrane color, respiration, and heart rate.

In light of these circumstances, the anesthetic protocol for such a clinic must meet several important criteria. The drug administered to the cats must be non-technical to prepare and easy to administer to conscious feral cats confined in traps. Anesthetic induction must be rapid. A predictable plane and duration of anesthesia and analgesia are required. The anesthetic must have a low mortality rate associated with its use.

The TKX anesthetic combination is reconstituted easily, requiring no expensive or technical anesthetic equipment. As an injectable anesthetic that requires only a small volume to be effective, TKX can be given to a fractious cat quickly without requiring manual restraint. The Food and Drug Administration has approved the use of tiletamine-zolazepam, ketamine, and xylazine as individual agents in cats. However, the anesthetic combination and the use of yohimbine represent off-label use of the drugs, and stability tests of the mixture have not been performed. All of the components of the TKX anesthetic combination are readily available from drug manufacturers. The Drug Enforcement Agency regulates 2 of its components, ketamine and the tiletamine-zolazepam combination, requiring them to be properly secured and their use documented. An ideal drug for feral cat clinics must also be inexpensive. In 2001, use of TKX cost < \$2/cat on the basis of a mean dose of 0.27 ml of TKX and 0.25 ml of yohimbine/cat.

The anesthetic protocol used in feral cats should provide rapid loss of consciousness, sufficient duration of anesthetic effects, and predictable results in every cat. Previous research³ on the use of TKX for declawing and castrating cats has revealed that TKX causes lateral recumbency within 5 minutes, with the anesthetic effects lasting approximately 40 minutes. Our study on the use of TKX in feral cats has yielded consistent results with TKX as evidenced by the mean dose of drug and number of doses required for each cat. Overall, 4,584 (79.5%) of the cats in our study required only 1 dose of TKX, with a mean dose of 0.24 ± 0.042 ml/cat. In addition, the drug dosages and anesthetic effects were uniform in most cats in various conditions (cryptorchid, previously neutered, and routine surgeries), with the exception of a larger volume used for pregnant females. The increased mean volume administered to pregnant females, but not an increased number of injections, was most likely attributable to their increased estimated body weight.

Most importantly, the anesthetic used must be safe with a low mortality rate. Few reports have been published regarding anesthetic death rates for dogs and cats. A large retrospective study¹⁴ of anesthesia in cats reported a mortality rate of 0.3% (34/11,227), which is similar to the results of our study. More than 75% of the cats in that survey were classified as young and healthy, and most were not weighed (82%), sedated (74%), or intubated (93%). Induction and maintenance of anesthesia was mainly with injectable anes-

thetics. A second retrospective study¹⁵ based on the recollections of small animal veterinarians in Vermont regarding anesthetic practice reported a mortality rate of 0.11% in dogs and 0.06% in cats. Ketamine used alone or in combination with other drugs such as xylazine or acepromazine was used most commonly. Most of the cats in that study were premedicated, although most (74.5%) were not intubated. Another retrospective study¹⁶ reported a mortality rate of 0.10% (1/1,016) in dogs and 0.14% (2/1,459) in cats when the computerized abstracts of medical records and a random sample of paper medical records of cats and dogs that had undergone elective ovariohysterectomies, castrations, and onychectomies were examined at a veterinary teaching hospital. In another retrospective study¹⁷ examining postoperative complications following the same types of elective surgeries at private practices, no deaths were reported among 935 cats and 646 dogs that underwent surgery.

A prospective study¹⁸ of anesthesia in small animal practice revealed that 0.15% (1/679) of dogs and cats died primarily because of anesthetic complications. The overall mortality rate for dogs was 0.23% (1/434) and 0.29% (1/340) for cats. In a second prospective study,¹⁹ 66 small animal practices in Ontario, Canada participated in a study to evaluate morbidity and mortality related to anesthesia. The overall mortality rate for dogs was 0.11% (1/899) and 0.1% (1/967) for cats. Lastly, in a prospective anesthetic mortality study at a veterinary teaching hospital, a mortality rate of 0.43% (11/2,556) was reported in dogs and 0.43% (3/683) in cats.²⁰

Summarizing these reports, it appears that the expected mortality rate in cats caused purely by anesthetic complications is approximately 0.0 to 0.4%. In our study, a total mortality rate of 0.35% was found, and the mortality rate suspected to be attributable solely to anesthesia was 0.23%. The mortality rate in this study is comparable to other studies, despite the large scale of the clinics and the fact that cats in this study had no physical examination, no laboratory evaluation, an unknown history, sometimes poor body condition, and were often highly stressed prior to anesthesia. Thus, on the basis of results of this study TKX can be judged as an acceptable injectable anesthetic for use in feral cat neutering clinics.

^aAmerican Pet Products Manufacturing Association, National Pet Owner Survey, 1999–2000.

^bAVMA Policy Statements and Guidelines, Position on Abandoned and Feral Cats, Approved by the AVMA Executive Board, 1996.

^cFeral Cat Coalition, San Diego, Calif.

^dOperation Catnip in Raleigh, NC, and in Gainesville, Fla.

^eTelazol, Fort Dodge Animal Health, Fort Dodge, Iowa.

^fKetaset, Fort Dodge Animal Health, Fort Dodge, Iowa.

^gXyla-ject, Phoenix Pharmaceutical Inc, St Joseph, Mo.

^hYobine, Lloyd Laboratories, Shenandoah, Iowa.

ⁱSawyer DC, Rech RH, Durham RA. Does ketamine provide adequate visceral analgesia when used alone or in combination with acepromazine, diazepam, or butorphanol in cats? (abstr), in *Proceedings. 4th Int Congr Vet Anaesth*, 1991;381.

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Correction: Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs

In “Clinical evaluation of dietary modification for treatment of spontaneous chronic renal failure in dogs” (*J Am Vet Med Assoc* 2002;220:1163–1170), the vertical axes of Figures 1 and 2 should read “Uremic crisis (cumulative % unaffected),” and the vertical axes of Figures 3 and 4 should read “Deaths (cumulative % survival).” In Figure 3, a renal-related death in the RF group should appear at day 615. In Figure 4, the data point at 450 days should be deleted from the survival curve for the RF group. In Table 3, in the second column, under the heading “RF,” the value corresponding to “Serum creatinine 2.0–3.0 mg/dl” should read “2/11 (18),” and the value corresponding to “Serum creatinine \geq 3.1–7.6 mg/dl” should read “5/10 (50).” In the third column, under the heading “MF,” these values should read “5/9 (56)” and “6/8 (75),” respectively. In the second paragraph in the second column on page 1167 the sixth sentence should read, “When the study was terminated, 82% of the dogs in the RF group had not yet developed the end point (uremic crisis), compared with 44% of dogs in the MF group (Table 3).”