COMPANION OR PET ANIMALS

Effectiveness of the anaesthetic combination of tiletamine, zolazepam, ketamine and xylazine for the sterilisation of street dogs in field clinics

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SUMMARY
15 dogs presented to a sterilisation clinic in March 2017 for ovariohysterectomy or castration surgeries. All patients were initially injected with an anaesthetic combination of Telazol (tiletamine/zolazepam), ketamine and xylazine (TKX) intramuscularly, followed by venous catheterisation and a number of follow-up intravenous boluses of TKX when appropriate to maintain a surgical anaesthesia. 6 dogs required redosing of the TKX drug combination. Data of monitoring anaesthesia via heart rate, respiratory rate, jaw tone, limb and muscle movement were collected. These data were used to determine timing for additional intravenous half doses of TKX for the maintenance of anaesthesia. All surgeries were successful without complications, and the anaesthetic protocol was effective at maintaining surgical anaesthesia. This case report describes a group of patients in which TKX was used as the anaesthetic protocol, with details on this previously unreported protocol such that others may be able to consider using TKX in future dog sterilisation clinics.

BACKGROUND
Sterilisation clinics to address dog and cat overpopulation issues have used many different anaesthetic protocols. While inhalational gas anaesthesia with isoflurane and oxygen may offer reliable and controllable forms of general anaesthesia, this form of anaesthesia is not often available for field sterilisation clinics. Instead, total intravenous anaesthesia (TIVA) is often used due to the ready availability of certain anaesthetic drugs and the ease of administration. This form of anaesthetic without the use of gas anaesthesia machines or oxygen tanks. Several protocols of TIVA exist, using different combinations of drugs. Selecting the best protocol for a field sterilisation clinic is dependent on clinicians’ knowledge of the pharmacology of the available intravenous anaesthetic drugs. Use of a protocol in practice by clinic team members can be done effectively once the clinic team members learn the effect of the drugs and how to determine when redosing is appropriate.

CASE PRESENTATION
Fifteen street dogs presented to a field sterilisation clinic in Chetumal, Mexico, in March 2017. The municipal veterinarian had approval from the Mayor of Chetumal to implement the clinic and use the proposed Telazol (tiletamine/zolazepam), ketamine and xylazine (TKX) anaesthesia protocol and to collect data. Twelve of the dogs were female and three were male. Ovariohysterectomy was to be performed on female dogs and orchietomy on male dogs. All of these dogs were dentally and skeletal mature, and vital signs (heart rate, respiratory rate and temperature) and basic physical examination, including body condition scores, were performed. Patients that were fractious had muzzles placed before examination. Dogs that continued to be very fractious even when muzzles were placed did not undergo a physical examination. All patients that were examined had vital signs within normal limits and had body condition scores between 3.5 and 4.0 out of 9. The dogs were weighed on a human bathroom scale. The dogs were held in the arms of a volunteer and their weights were recorded after subtracting the weight of the human volunteer. Any dogs that had a heart murmur greater than 2/6 were excluded from the clinic, as were dogs that were exhibiting signs of severe, chronic or infectious diseases. Vials of lyophilised tiletamine–zolazepam (230 mg tiletamine HCl and 250 mg zolazepam HCl) were reconstituted with 4 mL of ketamine HCl (100 mg/ml) and 1 mL of xylazine (100 mg/ml). Each millilitre of TKX contained 50 mg of tiletamine, 50 mg of zolazepam, 80 mg of ketamine and 20 mg of xylazine. Dogs were given an initial intramuscular dose of 0.044 mg/kg of TKX (2.2 mg/kg ketamine, 2.2 mg zolazepam, 3.52 mg ketamine and 0.88 mg xylazine/kg) to achieve anaesthetic induction. The intention was to deliver the drugs intramuscularly into the thigh muscles. A syringe pole was used to administer drugs through the door of a kennel to some aggressive individuals, and this route could not be confirmed.

After chemical immobilisation was achieved, an intravenous catheter was placed in the cephalic vein of each dog and a 4.4 mg/kg dose of injectable tramadol (50 mg/ml) was administered as an analgesic premedication. Meloxicam (0.2 mg/kg) was administered subcutaneously. Dogs were intubated and breathed room air. Lactated Ringer’s solution was administered intravenously during surgery at a rate of 5 ml/kg/hour. Record of anaesthetic monitoring was initiated when the dogs were secured to the surgical table and prepped for surgery. An example of the data recording sheet is in figure 1. Monitoring parameters were recorded every 10 minutes. Heart rate, respiratory rate, mucous membrane colour, capillary refill time, pulse quality and the frequency of redosing were recorded. An
Data recording sheet for patients under TKX intravenous anaesthesia. TKX, Telazol (tiletamine/zolazepam), ketamine and xylazine.

Table 1 Data of the patients regarding the time between initial administration of TKX anaesthesia intramuscularly to the time, if needed, when a redose was necessary.

<table>
<thead>
<tr>
<th>Weight of patient (kg)</th>
<th>Initial dose intramuscular (ml)</th>
<th>Redose Necessary?</th>
<th>Redose time from initial dose (minutes)</th>
<th>Redose Amount (ml)</th>
<th>Total anaesthesia dose (ml)</th>
<th>Procedure time (minutes)</th>
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Average redose time: 24.7 minutes. Average anaesthesia time: 48.4 minutes. Percentage of patients requiring redose: 40 per cent.

Figure 1 Data recording sheet for patients under TKX intravenous anaesthesia. TKX, Telazol (tiletamine/zolazepam), ketamine and xylazine.

Figure 2 Administering and monitoring Telazol (tiletamine/zolazepam), ketamine and xylazine total intravenous anaesthesia to a canine patient during a field sterilisation clinic.

Example of monitoring and dosing TKX anaesthesia is shown in figure 2. Six of 15 dogs required redosing based on observations of limb movement, increased heart rate, respiratory rate, palpebral reflex and jaw tone. Five dogs received an additional half dose of the initial dose administered intravenously through the peripheral intravenous catheter. One dog received a full dose, as the dog moved significantly, suggesting waking up from anaesthesia. Also, one dog received two half doses throughout the procedure. This may have been due to perhaps an initial intramuscular dose that was not given completely. Table 1 shows the data of the patients in the case series regarding the time between initial administration of TKX anaesthesia intramuscularly to the time, if needed, when a redose was necessary.

On average, for the six patients that needed a second dose, the time was 24.7 minutes from the initial dose.

Average anaesthesia time, from the point when the intramuscular injection was made to the time when the skin incision was closed, was 48.4 minutes. The weights of the patients varied from 8 to 31 kg. Propofol was available to give if stable anaesthesia was not achieved via the TKX combination but was not needed in any of the patients. Evaluation of respiratory and heart rates were conducted using a stethoscope and observation of condensation within the tracheal tube or rising and falling of the body wall. No other additional monitoring equipment was used. Nociception was inferred by changes in measured variables, such as heart rate and respiratory rate, or spontaneous movement in response to surgical manipulation which would cause pain, such as the manipulation of the suspensory ligament, or incising or transecting tissues. It was not observed that heart rate or respiratory rate appreciably increased in these surgical manipulations in the patients in this case series. In the event that respiratory depression occurred, defined as respiratory rates below 8 breaths/minute, an ambu bag was used to manually ventilate the patient. If bradycardia occurred, defined as heart rate of less than 40 beats/minute in dogs, partial reversal of the effects of xylazine with yohimbine was administered. Hypothetically, if
stable anaesthesia was not maintained in a patient, even under multiple doses of TKX, the intravenous catheter would be checked for patency. If that was not the issue, if a patient still was not maintained under anaesthesia, the initial intramuscular dose of TKX could be administered intravenously to produce stable anaesthesia. A lidocaine splash block (approximately 0.25 ml) was administered to female dogs after closure of the linea alba. Parameter recording stopped after dogs were moved to recovery mats for recovery and extubation once the patients showed signs of a gag reflex. Several anaesthetists throughout the case series were trained and implemented the TKX protocol, monitored the patients and collected the data while constantly being supervised by the authors. Body temperatures of the patients were not monitored during the procedure; however, during recovery, every patient returned to normal body temperature within 10 minutes.

OUTCOME AND FOLLOW-UP

Based on analysis of 15 dogs monitored at a small field sterilisation clinic run by FARVets International in Chetumal, Mexico, no deaths or anaesthetic complications were observed. Thirty-three per cent of dogs required administration of a half dose of TKX (0.022 ml/kg) less than 10 minutes after surgical start time. This may have been due to preparation time, which was not accounted for in the study. Forty per cent of dogs required at least one additional half dose of TKX after 30 minutes or less of surgical time. One dog needed an additional half dose at 80 minutes after initial dose due to the length of the surgery. Thirty-three per cent of dogs experienced prolonged capillary refill time (greater than 3 seconds). Seven dogs experienced transient or persistent tachypnoea (respiratory rate greater than 40 breaths/minute) for an average of 30 minutes. All other parameters monitored, such as heart rate, remained within normal physiological and clinical ranges. No dogs experienced excessive dysphoria, such as vocalisation or thrashing movements on recovery.

DISCUSSION

The number of free roaming owned or feral street dogs internationally is difficult to determine and varies widely, depending on government intervention, local culture and availability of sterilisation (ovariohysterectomy/orchiectomy) programmes. However, the WHO estimates the number of stray dogs worldwide to be approximately 200 million. Most street dogs are sexually intact and contribute substantially to the millions of dogs that are euthanised by municipal agencies every year. Additionally, these animals contribute to the spread of zoonotic disease, such as parasitism and rabies. Dogs also spread disease (distemper and parvovirus) to local wildlife populations. Although statistical analysis suggests that euthanasia campaigns may reduce street dog populations as rapidly as sterilisation over time, public backlash and the concerns of humane organisations have prevented the former tactic from being used in many locations.1

Street dog overpopulation issues have demanded veterinary intervention in the form of sterilisation campaigns, often conducted in remote areas where many anaesthetic agents are unavailable. Anaesthesia of street dogs presents unique challenges. Age, history, body weight and health conditions are often unknown. Dogs may be malnourished, suffering from infectious or systemic disease and heavily parasitised. The unpredictable temperament of street dogs and unknown vaccination status prevents examination prior to anaesthetic induction. Anaesthetic protocols for street dogs must prioritise the safety of the dogs and human clinic participants. Injectable anaesthesia allows handlers to administer immobilising drugs while animals are briefly restrained, or if necessary while contained in kennels via the use of a syringe pole. This eliminates the risk of escape or injury from potentially dangerous animals. The ideal injectable anaesthetic agent for these clinical settings is delivered in a small volume, results in rapid anaesthetic induction, provides a surgical plane of anaesthesia, has a predictable and sufficient duration of effect, has a rapid recovery, provides adequate postoperative analgesia and has a wide margin of safety.2,3

In order to use TIVA combinations effectively, the pharmacology and adverse effects must also be discussed and learnt, in addition to dosages and indications. Descriptions of the pharmacology and adverse effects of TKX are described here. TKX is a drug combination introduced over 20 years ago for high-volume sterilisation of domestic cats.4 This protocol has not yet been formally discussed for TIVA in dogs; however, it has been used previously in cats. The combination is administered intramuscularly as a premixed drug combination consisting of tiletamine HCl (equivalent to 250-mg free base) and zolazepam HCl (equivalent to 250-mg free base) as lyophilised powder in a 5-ml vial reconstituted with 40 mg (4 ml of 100 mg/ml) ketamine and 100 mg (1 ml of 100 mg/ml) xylazine HCl. The anaesthetic combination of TKX is unorthodox. TKX is a combination of two dissociative anaesthetics and two sedatives: zolazepam and xylazine. In doing so, TKX provides anaesthesia and multimodal analgesia. The TKX combination creates balanced anaesthesia by targeting distinct drug receptors in the CNS to reduce the volume of each drug and providing superior analgesia and anaesthesia than would be achieved when administered as sole agents. The practice of reconstituting the tiletamine–zolazepam with the other components results in a very small volume of drug being required to achieve anaesthetic induction. A reduction in the total volume required to be administered initially intramuscularly may help to prevent muscle damage and pressure necrosis.

Tiletamine–zolazepam is an injectable anaesthetic combination of a dissociative with a benzodiazepine. Tiletamine is a dissociative agent that produces analgesia, immobilisation and general anaesthesia. Zolazepam is a benzodiazepine anxiolytic that produces muscle relaxation. It is licensed for use in cats but not dogs, although it is commonly used in dogs and many other species. The combination may cause pain after intramuscular injection, transient tachycardia in dogs and athetoid movements, and can produce rough recoveries as the benzodiazepine is metabolised faster than the dissociative component in canids.5 In this case series, the anaesthetists did not observe transient tachycardia.

Ketamine is a rapidly acting dissociative general anaesthetic with significant analgesic activity through its disruption of N-methyl-D-aspartate (NMDA) receptors in the central nervous system.6 Ketamine increases sympathetic tone including cardiac output, heart rate, mean aortic pressure, pulmonary arterial pressure and central venous pressure. Ketamine can cause apneustic breathing patterns (rapid breaths followed by breath holding) and bronchodilation. Like tiletamine, it can lead to rough recoveries in dogs. Dogs may experience transient or persistent tachypnoea (respiratory rate greater than 40 breaths/minute) throughout anaesthesia, a common side effect of dissociative agents.6 Ketamine is not Food and Drug (FDA) licensed for use in dogs, although it is commonly used in dogs and many other species. As stated previously, seven dogs in this case series experienced tachypnoea that resolved after an average of 30 minutes.
Xylazine is a potent alpha2-adrenergic agonist that has actions both as a sedative and analgesic with muscle-relaxant properties. Xylazine can have some alpha1-agonist activity. The most common effects seen with xylazine administration are emesis, especially in cats, and bradycardia with reduction of cardiac output by up to 30 per cent.\(^6\) Dogs may experience prolonged capillary refill time (greater than 3 seconds), likely due to peripheral vasoconstriction secondary to xylazine administration. Xylazine is less commonly used in small animals as the development of dexmedetomidine, a more specific \(\alpha_2\) agonist, has replaced it in injectable drug combinations, because it is less likely to cause emesis and has more predictable anaesthetic durations and effects. However, dexmedetomidine is more potent, and xylazine has a wider safety margin in terms of dosing.\(^4\) However, in many international locations, dexmedetomidine is either unavailable, cost prohibitive or illegal. Capillary refill time in all patients in this case series were less than 2 seconds each time they were observed.

Due to the complicated interaction of the contradicting effects of this drug protocol, many of the adverse side effects of the individual components of the combination drug protocol were not observed. For example, xylazine may cause bradycardia, but due to the effects of the dissociatives that cause tachycardia, this negated the bradycardia that may have occurred if xylazine was used alone.

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) that is used in many perioperative drug protocols for analgesia and to reduce inflammation. It is a Cox-2 preferential drug that inhibits cyclo-oxygenase and prostaglandin synthesis. Adverse effects include vomiting and diarrhoea. Renal toxicity appears to be quite low in animals with normal renal blood flow.\(^6\) All patients in this case series received intravenous fluid therapy from induction of intravenous anaesthesia until completion of the surgery.

Local anaesthetics such as lidocaine and bupivacaine have been used as part of the anaesthetic and analgesic drug combination protocol to assist in providing analgesia post operatively.\(^7\) Lidocaine blocks sodium ion channels on nerve cell membranes, altering action potential propagation, leading to loss of nerve function including sensing pain.\(^6\) Lidocaine applied topically provides effective analgesia following ovariohysterectomy in the dog.\(^2\)

TKX is not FDA licensed for cats in combination, although each individual drug is FDA approved in cats.\(^2\) The use of TKX in feral cats has been shown to be economical, easily administered, with a low mortality.\(^2\) Because ketamine can cause increased muscle rigidity in dogs, it was thought to result in rough recoveries, and TKX has not been commonly used for anaesthesia in canids in the USA.\(^8\) Throughout this study, however, increased muscle rigidity was not observed in the patients. Due to the muscle-relaxant properties of xylazine as mentioned previously, muscle rigidity did not occur.

This study examines the use of the TKX combination with the addition of an NSAID and tramadol as a total injectable anaesthesia combination for international street dog sterilisation clinics. The use of TKX in street dogs has proven to be economical and easily administered with predictable effects. No information has been published to date on the effects of this drug combination in dog populations. The aim of this case study was to evaluate the anaesthetic and physiological effects of TKX in dogs undergoing sterilisation at small international field clinics that typically handle 10–15 dogs per day.

Based on preliminary findings, dogs were often tachypnoeic during anaesthesia with prolonged capillary refill time frequently observed. As noted previously, the heart rates of all patients remained within the normal ranges for dogs (70–160, depending on the size of the dog). Redosing of TKX to maintain a surgical plane of anaesthesia at half the initial induction dose can be expected in many dogs every 30 minutes or less.

The monitoring methodology in this case series was selected based on previous similar studies and guidelines, as well as to generally mimic monitoring situations that would occur in the locations where such an anaesthetic protocol may be used. Advanced physiological monitoring is certainly warranted, but in this case series, such instruments were not available and the guidelines of previous studies were followed.

TKX anaesthesia protocols have been previously studied in cats but not in dogs. In the study in cats,\(^7\) it is recognised that in some clinic settings, monitoring with specialised equipment is not feasible. The cats anaesthetised in that study were monitored during the clinics by assessment of mucous membrane colour, respiration and heart rate. The Association of Shelter Medicine veterinary medical care guidelines for spay-neuter programmes states that to ensure maintenance of an adequate plane of anaesthesia, individual patients must be carefully monitored and that the most reliable means to ensure ongoing patient assessment and safety during anaesthesia is vigilant monitoring by trained observers. In general, monitoring of several variables is required to accurately assess anaesthetic plane, and identification of changes in vital parameters is critical to an accurate assessment and that failure to recognise changes in variables can lead to an inadequate plane of anaesthesia or, conversely, to an excessive depth of anaesthesia, increasing the risk of complications, including death. The use of monitoring equipment must never replace vigilant, hands-on monitoring by educated observers.\(^9\)

Depending on individual circumstances, monitoring should involve assessment of various combinations of the following parameters: pulse, respiratory rate and pattern, jaw tone, eye position and pupil size, and palpebral reflex.\(^8\) These established parameters indicate that physiological stability can be maintained throughout surgery as stated earlier without using advanced monitoring equipment. In the patients in our case study, similar physiological stability was maintained, given the proven monitoring parameters of physical examination.

Future data collection will include body temperature at the completion of surgery, time to anaesthetic induction and time to extubation. In addition, data such as blood pressure and pulse oximetry may be collected, but because anaesthesia protocols such as TKX are performed in locations and conditions with limited resources, the type of data collected may be kept to that which can be measured using readily available tools, such as a stethoscope and physical examination of anaesthesia.

Although the anaesthetists were trained in using the TKX protocol, there may be some minor variation in the interpretation of anaesthetic depth and state of recovery of each patient. Each anaesthetist consulted with one of the authors of the paper when redosing, and when individual patients were deemed to be successfully recovered postoperatively. Another limiting factors in the report of this case series is the lack of large case numbers that would have included more data points.

This case series shows that the TKX combination is effective at inducing and maintaining surgical anaesthesia, and in our case series, we have not observed fatalities or major complications with this particular protocol at the stated dosages. We acknowledge that there are other drug combinations that have more established safety margins, such as Telazol/Forbugesic/dexmedetomidine.\(^8\) Dexmedetomidine, compared with xylazine, imparts less nausea and emesis. However, in many places abroad, neither
In many instances in sterilisation clinics in the field, gas anaesthesia may not be available. Total intravenous anaesthesia (TIVA) can be an effective part of anaesthesia and analgesia for performing sterilisation surgeries. Telazol (tiletamine/zolazepam), ketamine and xylazine (TKX) is an effective combination for TIVA in dogs. TKX in this instance has provided TIVA at surgical levels for various durations in dogs. In some cases, no redosing was necessary, and in others, redosing can be done to maintain surgical anaesthesia.

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REFERENCES