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Comparison of two sedation protocols for short electroretinography in cats

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Abstract

Objectives The objectives were to compare two different sedative combinations, xylazine–ketamine and dexmedetomidine–ketamine, on the short electroretinography (ERG) protocol and their impact on sedative effect, reversal times and physiological variables in cats.

Methods Six healthy spayed female domestic cats were sedated using one of two ketamine-containing protocols: intramuscular xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK). A short ERG protocol was recorded from the left eye of each cat under XK and DK sedation. Thirty minutes later, the effects were reversed with yohimbine or atipamezole for the XK and DK treatment, respectively. The cats were evaluated for time to recumbency, time to head elevation, and time to standing position after reversal treatments. Other variables recorded were: systolic blood pressure, cardiac rhythm, heart rate, pulse oximetry and respiratory rate. Recorded ERG variables included a- and b-wave amplitudes and implicit times under photopic, scotopic and scotopic mixed ERG conditions.

Results Time to lateral recumbency with XK was shorter than for DK ($P < 0.05$). After reversal, head elevation and standing position times were significantly longer for the XK than the DK group ($P < 0.05$). Heart rate increased and systolic blood pressure decreased from baseline in both groups ($P < 0.05$), but there were no significant differences between treatment groups. The b-wave amplitude recorded in the photopic study of cats treated with XK was lower than in animals treated with DK ($P < 0.05$). No other significant differences in ERG variables were observed between treatment groups ($P > 0.05$).

Conclusions and relevance The present study shows that XK and DK treatments are chemical restraint alternatives for ERG recording in cats, with only significant differences in the photopic b-wave amplitude.

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Introduction

Retinal examination is usually performed by means of indirect ophthalmoscopy combined with electroretinography (ERG) in order to assess retinal function. Full field flash ERG analysis is currently a well-established test to assess retinal function in cats with chorioretinitis; taurine deficiency retinopathy and other metabolic conditions; hypertensive retinopathy; optic neuritis;[1] drug-associated retinal toxicity;[2] and, less frequently, inherited rod–cone dysplasia, dystrophy and degenerations.[3,4] ERG is also used to assess retinal function in patients with opaque media and rule out generalized retinal diseases in patients with sudden loss of vision, even in the early phase of diseases when there may be no gross fundic changes.[5] Furthermore, ERG is an important tool in ophthalmological research, and

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pharmaceutical and toxicological screening for assessing deleterious side effects of drugs and other chemical compounds on the retina.[6,7]

Because ERG is sensitive to changes in retinal electrical current, it is crucial to avoid noise or artifacts associated with blinking, eyelid twitch, and globe or body movements. Patient movement may result in changes in the waveform, potentially leading to the misdiagnosis of retinal diseases.[8] In addition, during this study, patient handling should ensure that the electrodes remain in the proper position. Hence, sedation or general anesthesia is strongly recommended.[9–11]

Several anesthetic protocols, including thiopentone and propofol;[12] halothane or isoflurane, or sevoflurane with or without nitrous oxide;[13] ketamine combined with xylazine or medetomidine hydrochloride;[11,14,15] and tiletamine/zolazepam[16] have been used for ERG in dogs; and isoflurane,[4] ketamine combined with xylazine,[7,17–19] and pentobarbital[3] has been used in cats. As anesthetics may affect the ERG in a dose-dependent manner,[5] several studies have been performed in order to elucidate the effects of various anesthetics on the retina of dogs but not of cats.[9–11]

General anesthesia is typically used to perform ERG in animals, in order to restrict potential movements of the patient and its eyes. However, general anesthesia requires special equipment, monitoring and trained personnel, and it has inherent risks. Thus, the search for a simple, safe and effective drug combination is ongoing. In addition, some cats have species-specific aggressive behaviors where restraint may be difficult and stressful for the cat. Thus, sedation is common practice when performing an invasive procedure.

The combination of xylazine and ketamine is a classic technique accepted worldwide for chemical restraint in cats.[20] In recent years, dexmedetomidine has been introduced in veterinary medicine as an alternative alpha–2 (α_2) agonist for sedation in cats and dogs. Additionally, in cats, the use of the combination of this newer drug with ketamine has resulted in adequate sedation with minimal cardiovascular effects.[21] Both combinations are commonly used for the performance of ERGs at our teaching hospital, and we have not observed adverse reactions. However, the benefits of this combination of drugs and their impact on ERG performance have not been studied.

Our hypothesis for this study was that the α_2 agonist used would influence the ERG recordings and physiological variables in cats. To test this, the aim of the present study was to compare two different sedative combinations, xylazine–ketamine (XK) and dexmedetomidine–ketamine (DK), on the short ERG protocol and their impact on sedative effect, reversal times and physiological variables in cats.

Materials and methods

Animals

All procedures were carried out in strict accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. Six spayed female European shorthair cats (mean ± SD age 5.2 ± 0.6 years; mean ± SD weight 3.7 ± 0.7 kg) obtained from the colony for research at the Faculty of Veterinary Science, National University of the Center of Buenos Aires Province, Tandil, were housed individually under controlled temperature (22 ºC) and lighting (12 h light–dark cycle) conditions. Cats were adapted to human contact and procedures for 8–10 weeks before starting the study.

Physical, ophthalmologic, cardiovascular and respiratory health status were determined on the basis of a general, ocular, cardiovascular and respiratory examination on each animal. Ocular examination included Schirmer tear test measurements (Schirmer tear test strips; Schering-Plough Animal Health), fluorescein staining (Love Sudamericana Laboratory), applanation tonometry (Tono-Pen Vet; Reichert Ophthalmic Instruments), biomicroscopy (slit lamp HLS 150; Heine Optotechnik), and direct (Heine Beta 200; Heine Optotechnik) and indirect ophthalmoscopy (IO-α Small Pupil; Neitz Instruments). Cardiovascular and respiratory examinations included: electrocardiogram, heart rate, pulse oximetry, respiratory rate (Goldway UT 4000 F) and systolic blood pressure measurements (Parks Doppler Ultrasound Model 812; Parks Medical).

Experimental design

Following a crossover design the cats were randomly selected using a list randomizer.[22] The cats were treated under two different sedation protocols with a washout period of 2 days: (1) for the XK combination cats received xylazine hydrochloride (1 mg/kg; Xilacina 2%, Alfasan, Allignani) and ketamine hydrochloride (3 mg/kg; Ketamina 50, Holliday Scott) intramuscularly (IM); (2) for the DK combination cats received dexmedetomidine hydrochloride (5 µg/kg; Dexdomitor, Orion Pharma) and ketamine hydrochloride (3 mg/kg) IM.

All cats were fasted for a minimum of 12 h before administering the pharmacological treatments. The treatments were performed using a cat cage in a noiseless area under ambient light for 10 mins. Once the chemical restraint was achieved, a 22 G intravenous catheter was placed in a cephalic vein and the cats were positioned in sternal recumbency, with supplemental oxygen administration by a face mask (oxygen flow 3 l/min). Body temperature was measured by an intrarectal sensor and kept stable at 38 ± 1°C. The temperature was controlled by insulating the animal from the table and building a tent from blankets to trap heat and warm air

from hot-water bottles placed close to the animals. Thirty minutes after the treatment, the effects were reversed with IM yohimbine (0.5 mg/kg; Yohimbine Vet Up [Richmond]) or atipamezole (25 µg/kg; Antisedan [Pfizer]) following product-label recommendations for the XK and DK group, respectively. Sedation and reversal effects were evaluated recording time for recumbency after administration of sedation treatments (XK and DK) and time for head elevation and standing position after administration of reversal treatments (yohimbine and atipamezole), respectively.

Physiological variables evaluation

Physiological variables were registered at baseline and at 2 min intervals until 20 mins after treatment. We evaluated systolic blood pressure, cardiac rhythm, heart rate, pulse oximetry and respiratory rate. Systolic blood pressure was recorded by using a non-invasive Doppler technique (Parks Doppler Ultrasound Model 812; Parks Medical Electronics). For blood pressure measurement, the site of Doppler cuff placement was selected considering the requirements of the ERG recording procedure. Thus, a neonatal cuff was placed over the coccygeal artery on the tail, with the cuff width approximating 30% of the tail circumference based on previous studies reported in cats.[23,24] Measurements were performed by a single operator using an infant flat probe that was held manually at the same position over the artery. At each time point, blood pressure was measured five times; the average of these values was considered the systolic blood pressure for that time point. Pulse oximetry was measured using a probe placed on the front paw on each cat. Heart rhythm and rate was determined by a lead II electrocardiogram. These variables were automatically measured by a multi-parametric monitor (Goldway UT 4000 F). Finally, respiratory rate was counted from visualization of chest excursion during the respiratory cycle over a period of 1 min. Cats were kept in sternal recumbency during immobilization.

ERG procedure

Short ERG protocol was recorded from the left eye of each cat for XK and DK treatments. Phenylephrine hydrochloride (2.5%) and 1% tropicamide (Alcon Laboratories) and 0.5% sterile proparacaine hydrochloride ophthalmic solution (Anestalcon; Alcon Laboratories) were applied to both eyes to dilate the pupils and anesthetize the corneas, respectively. The corneas were intermittently irrigated with balanced salt solution (Alcon Laboratories) to prevent keratopathy. Each cat was placed facing the flash at a distance of 20 cm. Pupils were fully dilated throughout the examination, and pupil size was assessed at the start and end of the ERG examination. A commercial contact lens (ERG jet electrode; LKC Technologies) with a platinum wire was placed on the cornea as the active electrode, while the reference and grounding electrodes were a subcutaneous needle electrode placed on the ear and the occipital crest, respectively. Eyelids were fixed by use of a blepharostat. Briefly, in this short ERG protocol, the cats were prepared in ambient light and after 10 mins photopic recording was conducted. Then, the light was turned off and retinal function was tested within the first minute and after 5 mins of dark adaptation (scotopic). After that, there was an immediate scotopic examination, and scotopic mixed responses were evaluated. Two different stimuli were used for scotopic ERGs: scotopic low stimulus strength responses for rods, and scotopic standard stimulus strength responses for mixed rod and cone responses. The conditions for photopic and scotopic mixed ERGs were 10 responses to flash of white light (4 ms; 1 Hz) from a photic stimulator (light-emitting diodes) set at maximum brightness (350 candela s/m^2 without a filter). Signals were amplified, filtered (1.5 Hz low-pass filter; 3000 Hz high-pass filter; notch activated) and averaged (Akonic BIO-PC; Akonic). For scotopic evaluation the conditions were the same with a response to flash of white light (4 ms; 0.2 Hz). The implicit times and amplitudes of the a- and b-waves were measured for all ERGs. The a-wave amplitude was measured as the difference in amplitude between the recording at onset and the trough of the negative deflection, and the b-wave amplitude was measured as the difference in amplitude between the trough of the a-wave to the peak of the b-wave. ERG responses were averaged for each run (10 tests) in photopic and scotopic mixed ERGs and the mean values were used for subsequent analysis.

Statistical analysis

All data are presented as mean ± SD. Data were tested for normality using a Shapiro–Wilk test. Comparison between XK and DK treatments of time for recumbency, time for head elevation, time for standing position and ERG a- and b-latency, and amplitude wave was performed by means of paired Student's *t*-test. Two-way repeated MANOVA was employed to test for differences in heart rate, pulse oximetry, respiratory rate and systolic blood pressure between the animal groups (treatment), and also accounting for time as the second dependent variable. For all analyses, a value of $P < 0.05$ was considered significant.

Results

All cats tolerated the sedation protocol well and were not observed vomiting during or after the study. The sedative effect was sufficient for the ERGs instrumentation and recording in both treatments.

Sedative and reversal times

As shown in Figure 1(a), there was no difference between treatments in time to lateral recumbency. After reversal,

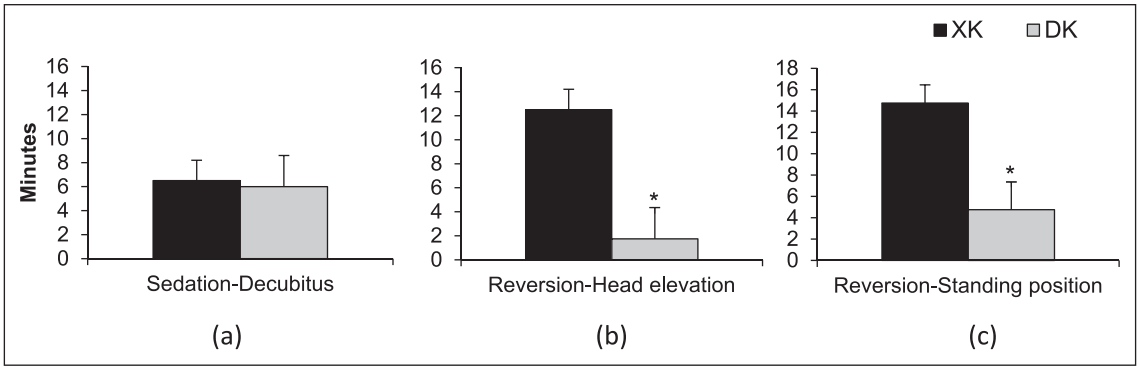

Figure 1 Time periods required for recumbency after (a) sedation, (b) head elevation or (c) standing position after reversal of cats administered xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK) intramuscularly (IM), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK) IM, and antagonized IM with yohimbine (0.5 mg/kg) or atipamezole (25 µg /kg) for the XK and DK groups, respectively. Data are shown as mean time ± SD.* $P < 0.05$, n = 6 cats

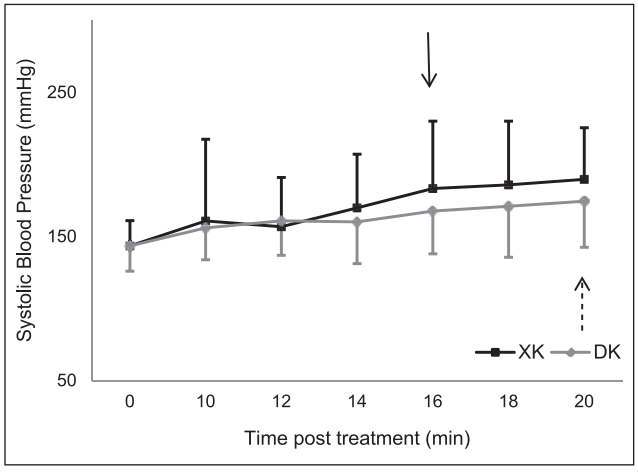

Figure 2 Systolic blood pressure (mm Hg) values measured in cats administred xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK) intramuscularly (IM), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK) IM. Data are shown as mean time ± SD (n = 6). Within treatments groups, a solid (XK) or dashed (DK) arrow indicates the time at which systolic blood pressure began to differ from values registered before sedation treatment (0 min; $P < 0.05$)

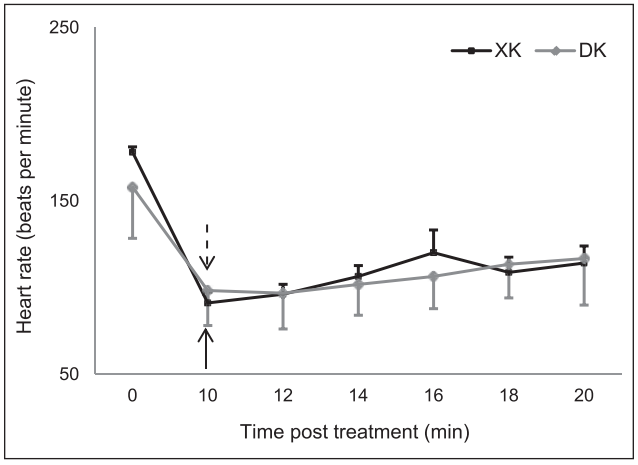

Figure 3 Heart rate values (beats/min) registered in cats administred xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK) intramuscularly (IM), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK) IM. Data are shown as mean ± SD (n = 6). Within treatments groups, a solid (XK) or dashed (DK) arrow indicates the time at which heart rate began to differ from values registered before sedation treatment (0 min; $P < 0.05$)

head elevation and standing position times were significantly longer for cats having the XK than those having DK treatment.

Physiological variables

The intramuscular administration of XK and DK resulted in a significant increase of systolic blood pressure and decrease of heart rate relative to baseline values, without significant differences between groups (Figures 2 and 3).

For pulse oximetry, the recorded values were >95% saturation at all times in both groups. Cardiac rhythm and respiratory rate stayed stable after treatment. All physiological variables evaluated were no different between treatments groups.

ERG

Amplitudes and implicit times of ERG a- and b-waves of cats sedated with XK or DK are shown in Table 1. No differences in ERG a- and b-wave amplitudes and implicit times were observed between XK and DK treatments, except for b-wave amplitude in the photopic study that was statistically lower in cats treated with XK than those

Table 1 Amplitudes and implicit times of a- and b-wave of photopic, scotopic and scotopic mixed electroretinogram in cats administered xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK) intramuscularly (IM), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK) IM

		Animal group	
		XK	DK
b-wave			
Amplitude	Photopic	19.3 ± 9.5*	22.9 ± 8.6
	Scotopic (1 min)	232.4 ± 75.2	199.7 ± 44.8
	Scotopic (5 mins)	294.1 ± 123.8	242.0 ± 30.1
	Scotopic mixed	212.3 ± 95.3	195.0 ± 21.5
Implicit time	Photopic	28.5 ± 3.4	29.5 ± 4.0
	Scotopic (1 min)	50.7 ± 15.1	50.0 ± 16.2
	Scotopic (5 mins)	40.5 ± 1.0	38.9 ± 4.0
	Scotopic mixed	35.1 ± 10.4	35.2 ± 10.9
a-wave			
Amplitude	Photopic	6.8 ± 6.3	7.9 ± 6.3
	Scotopic (1 min)	37.8 ± 1.0	36.7 ± 2.3
	Scotopic (5 mins)	56.4 ± 25.5	48.6 ± 17.3
	Scotopic mixed	39.0 ± 1.5	36.7 ± 5.4
Implicit time	Photopic	10.5 ± 1.5	10.6 ± 1.0
	Scotopic (1 min)	13.5 ± 0.6	13.2 ± 0.9
	Scotopic (5 mins)	14.2 ± 0.8	14.1 ± 1.0
	Scotopic mixed	14.5 ± 0.6	13.9 ± 0.7

Data are shown as mean ± SD
*P <0.05, n = 6

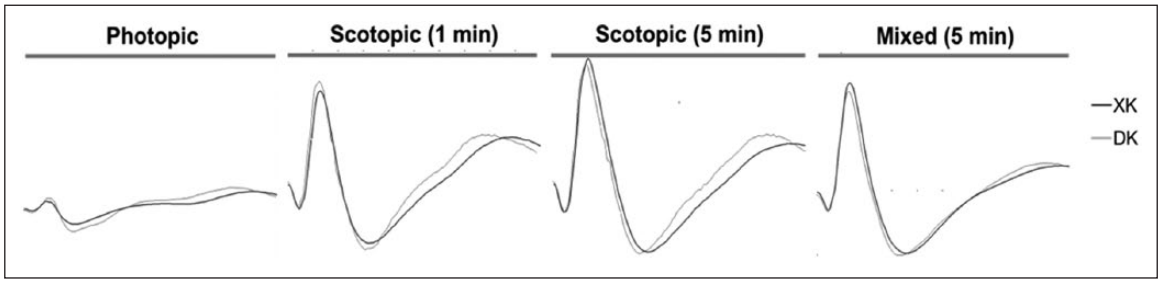

Figure 4 Representative electroretinogram response from a cat (n = 6) sedated intramuscularly with xylazine hydrochloride (1 mg/kg) plus ketamine hydrochloride (3 mg/kg) (XK), and dexmedetomidine hydrochloride (5 µg/kg) plus ketamine hydrochloride (3 mg/kg) (DK)

treated with DK. Representative photopic, scotopic and scotopic mixed ERG traces from the same cat for both groups are shown in Figure 4.

Discussion

In veterinary ophthalmology, ERG is used to diagnose acquired and inherited retinal diseases; assess retinal function in patients with opaque ocular media, such as cataracts; and exclude an outer retinal component in patients with retinal ganglion cell or post-retinal dysfunction. The ERG provides more objective results than ophthalmoscopy and characterizes the function of specific cell types in the retina. Furthermore, the ERG usually allows much earlier diagnosis of retinal disease than ophthalmoscopic or behavioral examinations.[5]

The high sensitivity of the ERG to movement and the lack of animal cooperation needed for the procedure demand a chemical restraint with sedatives or anesthetics. Most of the sedatives and anesthetics have depressant effects on ERG tracings in dogs and rats. In this context, it is relevant to study the impact of these drugs on ERG results in order to obtain ERGs similar to those without them. However, to our knowledge, there are no reports in cats.

We evaluated the effect of XK or DK sedative combinations on a short ERG protocol in cats. The sedative combinations chosen for this study were α_2-agonists

(xylazine or dexmedetomidine) and ketamine, a worldwide protocol for chemical restraint in cats.[20] Specifically, these combinations have shown optimal retinal function preservation in dogs and rats.[9,25] Additionally, these treatments avoid ventromedial rotation of the eyes, improving the quality of the study.

In previous studies in cats, time to lateral recumbency was not significantly different between treatments.[21] In our study, both treatments (XK and DK) elicited an adequate sedation level for the ERG instrumentation; the cats tolerated corneal electrodes without blinking or purposeful movements. Selected doses are commonly used for chemical restraint in cats. However, it is not possible to affirm that were equipotent sedative doses due to this study did not assess the degree of sedation.

In the present study, both combinations elicited significant decreases in heart rate in comparison with baseline values. The decrease in heart rate after administration of XK or DK combination is common in animals, and occurs as a result of the increased vagal tone mediated by central α_2-agonist and by hypertensive cardiac reflex. On the contrary, systolic blood pressure increased significantly compared with baseline values as a result of the peripheral vasoconstriction effect mediated by α_1- and α_2-receptors.[26] Specifically for dexmedetomidine, owing to the low α_1 selectivity, the hypertensive effect could be mainly related to a subtype of α_2-receptor.[27] However, neither heart rate nor systolic blood pressure was different between treatment groups.

In contrast to previous studies, respiratory rate modification was not observed under either sedative combination in the cats. Verstegen et al[28] demonstrated that administration of α_2-adrenoceptor agonists and ketamine led to respiratory depression in a dose-dependent fashion, proportional to the dose of dissociative anesthetic administered. Even though we used a low dose of ketamine (3 mg/kg), which could explain the lack of respiratory rate variation in our cohort of animals, we should mention that the cats used in this study were used to handling. As a consequence, they were not obviously stressed at the baseline measurement of respiratory rate.

While the ERG protocol most commonly used in cats is a very brief ERG protocol that determines whether a retinal response is present or absent, the short ERG protocol selected for this study offers a more comprehensive protocol, including selective rod and cone assessment, which could be used to diagnose generalized outer retinal disease.[5,8]

In the present study, the ERG examination was successfully completed under both sedative/anesthetic protocols in cats. The ERG variables obtained in our study showed that, except for lower b-wave amplitude under photopic conditions in animals treated with DK vs those treated with XK, no significant changes in a- and b-wave amplitude and implicit time were observed between XK and DK treatments. Nonetheless, the present results should be corroborated in a larger number of animals.

After reversal with yohimbine or atipamezole, for XK and DK, respectively, head elevation and standing position times were statistically shorter for DK treatment, providing a quicker recovery. In the present study a different reversal was used for each treatment; consequently, further studies are necessary to evaluate if the differences observed could be attributed to the reversal used or to the XK or DK treatments.

Conclusions

In the present study, sedation with XK or DK showed no significant differences for cardiovascular and respiratory responses and allowed the proper performance of diagnostic ERGs in cats. Except for the photopic b-wave amplitude, no significant differences were observed on ERG recordings between treatments. For further conclusions a larger number of animals should be used.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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