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RESEARCH PAPER

Characterization of the anesthetic effects of dexmedetomidine–vatinoxan–ketamine combinations in cats

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Abstract

Objective To characterize the anesthetic effects of dexmedetomidine, vatinoxan and ketamine combinations in cats.

Study design Randomized crossover experimental study.

Animals A group of seven healthy male neutered cats, with body mass 5.2 ± 0.4 kg and aged 1–2 years.

Methods Cats were implanted with a telemetric transmitter for remote recording of mean arterial pressure and heart rate before beginning the study. Each cat received a total of six treatments, coadministered in a single syringe, each at least 2 weeks apart: dexmedetomidine (25 μg kg^{-1}, D) + vatinoxan (600 μg kg^{-1}, V) + ketamine (2.5 mg kg^{-1}, K2.5) intramuscularly (IM) (DVK2.5IM); D + V + ketamine (5 mg kg^{-1}, K5) IM (DVK5IM); D + V + ketamine (10 mg kg^{-1}, K10) IM (DVK10IM); D + K5 IM (DK5IM); D + V + K5 subcutaneously (SC) (DVK5SC); or D + V + K5 intravenously (IV) (DVK5IV). Select physiologic variables and time to recumbency, immobilization, first movement, head lift, return to sternal recumbency and walking were recorded. Quality of sedation/anesthesia was assessed using a visual analog score. Response to noxious electrical stimulation was assessed at 10 minute intervals.

Results Heart rate (beats $minute^{-1}$) was significantly greater in DVK5IM (overall mean ± standard deviation 142 ± 19) than in DK5IM (115 ± 16). No treatment consistently prevented movement in response to noxious stimulation. Time to first movement was significantly shorter in DVK2.5IM (45 ± 10 minutes) than in DVK10IM (93 ± 25 minutes), and in DVK5IM (53 ± 12 minutes) than in DK5IM (95 ± 39 minutes).

Conclusions and clinical relevance Dexmedetomidine–vatinoxan–ketamine combinations, at the doses studied, may be useful to produce sedation, but do not appear to consistently produce anesthesia as characterized by immobility in response to noxious stimulation.

Keywords α_2-agonist, α_2-antagonist, anesthesia, cardiovascular, cats, sedation.

Introduction

Dexmedetomidine, a selective alpha-2 adrenergic receptor agonist, and ketamine, a cyclohexane NMDA receptor antagonist, are frequently administered together, with or without other adjuncts (opioids and/or other sedatives), to cats to achieve heavy sedation or anesthesia (Joyce & Yates 2011; Ko et al. 2011; Fernandez-Parra et al. 2017; Khenissi et al. 2017; Diep et al. 2020; Posner et al. 2020; Gomes et al. 2022a,b; Rufiange et al. 2022; Malo et al. 2023). Although dexmedetomidine provides sedation and analgesia and reduces requirements for other anesthetics, it also produces profound cardiovascular adverse effects (Pypendop et al. 2017; Jaeger et al. 2019). The desirable effects of dexmedetomidine (sedation, analgesia, reduction in anesthetic requirements) are owing to binding of receptors within the central nervous system (CNS), whereas the undesirable cardiovascular effects (vasoconstriction, bradycardia) are owing, at least in part, to binding of receptors outside of the CNS (Murrell & Hellebrekers 2005).

Vatinoxan (previously known as MK-467 and L-659066) is an alpha-2 adrenergic receptor antagonist that poorly penetrates the CNS (Clineschmidt et al. 1988; Honkavaara et al. 2020). When administered concurrently with

dexmedetomidine, it has been shown to attenuate dexmedetomidine-induced vasoconstriction and bradycardia in dogs (Honkavaara et al. 2011) and cats (Honkavaara et al. 2017a). Vatinoxan also shortens dexmedetomidine-induced sedation and decreases dexmedetomidine-induced reduction in the minimum alveolar concentration of inhaled anesthetics in both species (Pypendop et al. 2019; Hector et al. 2021). Nevertheless, as vatinoxan improves heart rate (HR) and cardiac output when administered concurrently with dexmedetomidine in dogs and cats, its use may be beneficial, particularly when using high doses of the agonist and/or in patients with pre-existing disease.

This study aimed to investigate the anesthetic effects of the dexmedetomidine—vatinoxan—ketamine combination in healthy cats. It was hypothesized that the addition of vatinoxan would reduce the effect of dexmedetomidine on HR and mean arterial pressure (MAP), and that the duration of anesthesia would be dependent on ketamine dose.

Materials and methods

The ARRIVE 2.0 reporting guidelines were followed (Percie du Sert et al. 2020).

Animals

A total of seven male, neutered, purpose-bred, research cats, with body mass 5.2 ± 0.4 kg [mean ± standard deviation (SD)] and aged 1—2 years, were enrolled in the study. Cats were determined to be healthy based on thorough clinical examinations before beginning the study (inclusion criterion). Cats were excluded from the study if they did not tolerate the handling required for the experiments. Cats were group housed in a room at the institution's Teaching and Research Animal Care Services facility under previously described husbandry conditions (Honkavaara et al. 2017a). Cats were fed a commercial diet (5003 Laboratory Feline Diet; LabDiet, MO, USA) once a day and had access to water *ad libitum*. Food was removed for at least 12 hours before experiments, but water remained available until approximately 20 minutes before drug injection. The study was approved by the Institutional Animal Care and Use Committee at the University of California, Davis (protocol 22861).

Instrumentation

At least 2 weeks before starting the study, each cat was anesthetized for implantation of a telemetric transmitter (Physiotel HD-S11; Data Sciences International, MI, USA), as previously described and presented in Appendix SA (Honkavaara et al. 2017a).

The day before each study, at least 12 hours before treatment injection, cats were anesthetized using isoflurane in oxygen delivered in an acrylic chamber. Once the righting reflex was lost, induction of anesthesia was completed by delivering isoflurane in oxygen via a facemask. The cat's trachea was intubated and anesthesia was maintained with isoflurane in oxygen, using a circle system and mechanical ventilation, as described above. A 22 gauge, 10 cm catheter (Central Venous Catheter; Mila International, KY, USA) was inserted in a jugular vein to allow blood sampling for measurement of drug concentrations (results reported separately). In addition, a 22 gauge, 4.4 cm catheter (Introcan Safety IV Catheter; B Braun, PA, USA) was placed in a medial saphenous vein [intravenous (IV) treatment only]. Light bandages were applied to protect the catheter(s), an Elizabethan collar placed and cats allowed to recover from anesthesia.

Treatments

On each of 6 study days, each cat was administered one of six treatments: dexmedetomidine (25 μg kg^{-1}, D) + vatinoxan (600 μg kg^{-1}, V) + ketamine (2.5 mg kg^{-1}, K2.5, Ketamine hydrochloride injection; Dechra, KS, USA) intramuscularly (IM) (DVK2.5IM); D + V + ketamine (5 mg kg^{-1}, K5) IM (DVK5IM); D + V + ketamine (10 mg kg^{-1}, K10) IM (DVK10IM); D + K5 IM (DK5IM); D + V + K5 subcutaneously (SC) (DVK5SC); or D + V + K5 IV (DVK5IV). All cats were administered the five IM and SC treatments in a randomized order generated by an online randomizer (www.random.org), with at least 2 weeks between treatments. IM injections were performed in the lumbar epaxial muscles and SC injections in a skin fold between the shoulder blades, caudal to the scar from telemetric transmitter implantation. The IV treatment was not randomized in the order sequence and always administered last. Vatinoxan was prepared each morning by diluting vatinoxan powder in isotonic saline (0.9% NaCl; Baxter Healthcare Corp., IL, USA) to a concentration of 10 mg mL^{-1}. The solution was filtered through a 0.22 μm filter (Fisherbrand Sterile Syringe Filter; Fisher Scientific, MA, USA) into a sterile syringe and mixed with the other drugs within 90 minutes of injection.

Data collection

On each study day, the transmitters were switched on and a signal repeater (Physiotel Large Animal Repeater; Data Sciences International) was secured to the cat with an elastic strap around the thorax. The transmitter signal was relayed to a receiver (Physiotel Receiver; Data Sciences International) and recorded by a computer equipped with the acquisition software (Dataquest Open-ART and Ponemah 5.1; Data Sciences International). Baseline physiologic variables [HR from ECG, MAP from carotid catheter and respiratory frequency (f_R) from visual observation] were collected at least 15 minutes before treatment.

Following injection of drugs and recumbency, cats were placed in lateral recumbency on a table and additional monitoring equipment was placed. A pulse oximeter probe (CARESCAPE B850, GE Healthcare or petMAP+ II, CardioCommand, FL, USA) was placed on the tongue, pinna or across a digit, whichever provided the best signal quality, for the measurement of arterial hemoglobin oxygen saturation (SpO_2). A 20 gauge, 5 cm catheter (Insyte; Becton Dickinson, NJ, USA) connected to a sampling line and capnograph (CARESCAPE B850 or Carestation 620) was inserted in the trachea so that the catheter hub was positioned immediately cranial to the glottis for the measurement of end-tidal partial pressure of carbon dioxide ($P_E'CO_2$). A handheld digital thermometer was inserted into the rectum. The ventral aspect of the proximal tail was clipped and 25 gauge needles placed SC approximately 2 cm apart and connected by alligator clips to an electrostimulation device (S88 Stimulator; Grass Instruments, MA, USA). All physiologic variables (HR, f_R, MAP, SpO_2, $P_E'CO_2$, temperature) were recorded at 5 minute intervals from drug delivery until the cat resumed sternal recumbency or became intolerant to the monitoring equipment, whichever occurred first. Noxious electrical stimulation (50 Hz, 10 ms, 25 V) (Eger et al. 1965) was applied until movement of the head or limbs was observed or 1 minute had elapsed, whichever occurred first, starting 10 minutes after drug administration and every 10 minutes thereafter, until three successive stimulations resulted in movement.

Times from injection to recumbency, immobility, first movement, head lift, sternal recumbency and walking were recorded. The quality of induction, maintenance and recovery from sedation/anesthesia was scored by an investigator (YHL) blinded to the IM and SC treatments using a visual analog scale (VAS) where 0 and 100 were the worst and best quality possible, respectively. At the time of head lift, meloxicam (0.3 mg kg^{-1}) was administered SC and all external monitoring instruments were removed.

At least 10 days after completion of all treatments, cats were anesthetized as for telemetric transmitter removal, using the same drugs and doses as for transmitter implantation. The hair was clipped and the skin prepared, and an incision was made over the transmitter. The transmitter was removed and the skin closed in two layers. Meloxicam (0.3 mg kg^{-1}) was administered SC and each cat was monitored daily for 10 days for signs of pain and infection. All cats recovered uneventfully and were offered for adoption.

Statistical analysis

Power analysis based on the mean and SD in HR at 60 minutes following IM injection of D or DV in a previous study suggested that seven cats would be sufficient to detect a 36 beats $minute^{-1}$ difference in HR between treatments (less than the mean difference in the previous study), with a power of 0.8 and the alpha level set at 0.05 (Honkavaara et al. 2017b).

Normality of data was verified using the Shapiro–Wilk test. Data that were not normally distributed were log-transformed before analysis. The effect of treatment on anesthesia times (time to lateral recumbency, time to immobility, time to head lift, time to return to sternal recumbency, time to walking) and on the total number of negative responses (i.e. no movement observed) to electric stimulation were analyzed using a repeated measures one-way analysis of variance followed by a Tukey test for pairwise comparisons where appropriate. The effect of treatment, time and their interaction on HR, f_R, MAP, SpO_2, $P_E'CO_2$ and temperature were analyzed using a mixed model, with time as a repetition and the cat as a random effect. Pairwise time comparisons with baseline (for variables measured at baseline) or with the first measurement (for variables not measured at baseline) within treatments were conducted using the Dunnett test. Pairwise treatment comparisons with DK5IM were conducted using the Dunnett test. The effect of treatment on VAS scores for quality of anesthetic induction, maintenance and recovery were analyzed using the Kruskal–Wallis test followed by the Steel test for pairwise comparisons with DK5IM where appropriate. The IV VAS data were excluded from analysis owing to the lack of blinding. The alpha level was set at 0.05. All analyses were conducted using commercial software (JMP Pro 17; SAS Institute, NC, USA). Data are presented as mean ± SD except VAS scores, which are presented as median (range). For significant differences, the mean difference and 95% confidence interval are presented.

Results

All cats recovered from all treatments uneventfully with no complications reported. Only one cat was excluded from the IV study as it became increasingly aversive to handling. Therefore, data are available for seven cats for the IM and SC treatments, and for six cats for the IV treatment. No arterial pressure measurement was obtained for all treatments in one cat. Additionally, MAP measurements were intermittently missing in four other cats. *P*-values for nonsignificant results and significant comparisons with baseline or first measurement are presented in Appendix SA.

Times

Times to recumbency, immobility, first movement, head lift, return to sternal recumbency and walking are presented in Fig. 1. A significant effect of treatment was found on time to recumbency ($p < 0.0001$), time to immobility ($p = 0.011$), time to first movement ($p = 0.003$), time to head lift ($p = 0.003$), time to sternal recumbency ($p = 0.001$) and time to walking ($p < 0.0001$). Time to recumbency was significantly longer for the SC treatment than for all other treatments

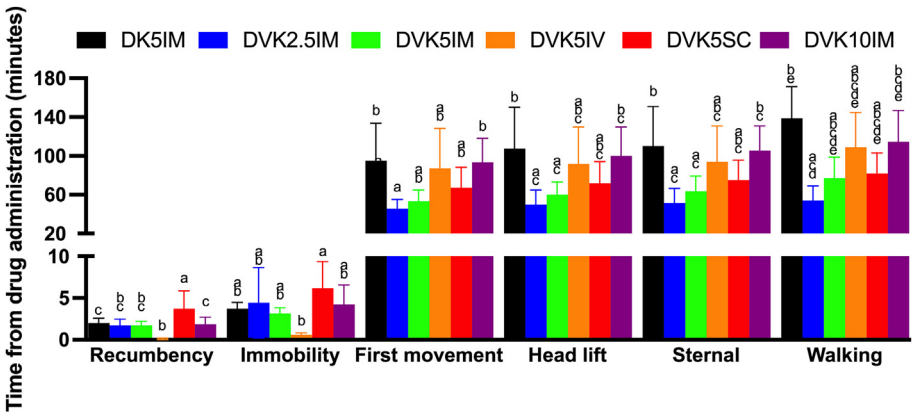

Figure 1 Time from injection to recumbency, immobility, first movement, head lift, sternal recumbency and walking in cats administered combinations of dexmedetomidine, vatinoxan and ketamine. D: dexmedetomidine 25 μg kg^{-1}; V: vatinoxan 600 μg kg^{-1}; K2.5: ketamine 2.5 mg kg^{-1}; K5: ketamine 5 mg kg^{-1}; K10: ketamine 10 mg kg^{-1}; IM: intramuscular; IV: intravenous; SC: subcutaneous. Drugs were mixed in the same syringe before injection. A total of six cats were administered DVK5IV and seven cats were administered all other treatments. Treatments with different letters are significantly different from each other ($p < 0.05$). Data are presented as mean (bar) and standard deviation (error bars).

[DVK5SC *versus* DVK2.5IM: 2 (0.3−3.7) minutes, $p = 0.013$; DVK5SC *versus* DVK5IM: 2 (0.3−3.7) minutes, $p = 0.013$; DVK5SC *versus* DVK5IV: 3.7 (1.9−5.4) minutes, $p < 0.0001$; DVK5SC *versus* DK5IM: 1.7 (0.02−3.4) minutes, $p = 0.046$; DVK5SC *versus* DVK10IM: 1.9 (0.2−3.6) minutes, $p = 0.025$]. In addition, time to recumbency was significantly longer for DK5IM [1.9 (0.2−3.7) minutes, $p = 0.024$] and DVK10IM treatments than for DVK5IV [1.8 (0.03−3.6) minutes, $p = 0.044$]. Time to immobility was significantly longer for DVK5SC treatment than for DVK5IV treatment [5.6 (1.4−9.8) minutes, $p = 0.004$]. Times to first movement, head lift, sternal recumbency and walking were significantly shorter in DVK2.5IM than in DK5IM [first movement: 49.4 (6.2−92.7) minutes, $p = 0.017$; head lift: 57.9 (11.7−103.9) minutes, $p = 0.007$; sternal recumbency: 58.9 (15−102.8) minutes, $p = 0.004$; walking: 85 (39.2−130.2) minutes, $p < 0.0001$] and DVK10IM [first movement: 48.0 (4.8−91.2) minutes, $p = 0.022$; head lift: 50.4 (4.3−96.6) minutes, $p = 0.025$; sternal recumbency: 54.1 (10.3−98.0) minutes, $p = 0.009$; walking: 60.4 (14.9−105.9) minutes, $p = 0.004$]. In addition, times to head lift, sternal recumbency and walking were significantly shorter in DVK5IM than in DK5IM [head lift: 47.4 (1.3−93.6) minutes, $p = 0.041$; sternal recumbency: 46.7 (2.8−90.6) minutes, $p = 0.031$; walking: 61.8 (15.6−14.6) minutes, $p = 0.005$]. Time to walking was significantly shorter in DVK5SC than in DK5IM [56.8 (11.3−102.3) minutes, $p = 0.008$], and in DVK2.5IM than in DVK5IV [54.7 (9.2−100.2) minutes, $p = 0.011$].

Response to electric stimulation

The number of negative (i.e. lack of movement) responses to electric stimulation is presented in Table 1. A significant ($p = 0.002$) effect of treatment on number of negative responses to electric stimulation was found. The number of negative

Table 1 Number of cats unresponsive to electric stimulation at different times after injection of combinations of dexmedetomidine, vatinoxan and ketamine. D, dexmedetomidine 25 μg kg^{-1}; V, vatinoxan 600 μg kg^{-1}; K2.5, ketamine 2.5 mg kg^{-1}; K5, ketamine 5 mg kg^{-1}; K10, ketamine 10 mg kg^{-1}; IM, intramuscular; IV, intravenous; SC, subcutaneous. Drugs were mixed in the same syringe before injection. A total of six cats were administered DVK5IV and seven cats were administered all other treatments. All cats responded at time 60 minutes and subsequent times (stimulation was not tested after three consecutive responses). The cumulative number of non-responses to electrical stimulation was significantly different in treatments marked with different letters ($p < 0.05$).

Time (minutes)	DK5IM	DVK2.5IM	DVK5IM	DVK5IV	DVK5SC	DVK10IM
10	6	2	4	3	0	5
20	4	1	3	1	0	5
30	4	0	0	0	0	3
40	3	0	0	0	0	1
50	0	0	0	0	0	1
Cumulative total	17^{a}	3^{bc}	7^{abc}	4^{abc}	0^{c}	15^{ab}

Table 2 Median (range) visual analog scale scores (mm) for quality of induction of, maintenance of and recovery from sedation/anesthesia in seven cats following injection of combinations of dexmedetomidine, vatinoxan and ketamine, with 0 and 100 representing the worst and best possible quality, respectively. D, dexmedetomidine 25 μg kg^{-1}; V, vatinoxan 600 μg kg^{-1}; K2.5, ketamine 2.5 mg kg^{-1}; K5, ketamine 5 mg kg^{-1}; K10, ketamine 10 mg kg^{-1}; IM, intramuscular; SC, subcutaneous. Drugs were mixed in the same syringe before injection.

	DK5IM	DVK2.5IM	DVK5IM	DVK5SC	DVK10IM
Induction	91 (86–94)	92 (88–94)	91 (70–94)	81 (69–92)	91 (79–95)
Maintenance	89 (78–90)	76.5 (66–92)	78 (57–94)	76 (57–84)*	91 (76–97)
Recovery	85 (80–95)	82.5 (77–88)	86 (64–92)	83 (69–90)	87 (83–94)

*Significantly different from DK5IM ($p < 0.05$).

responses to stimulation was significantly greater in DK5IM than in DVK2.5IM [2.0 (0.1–3.9) minutes, $p = 0.037$] and DVK5SC [2.4 (0.5–4.3) minutes, $p = 0.007$], and in DVK10IM than in DVK5SC [2.1 (0.2–4.1) minutes, $p = 0.021$].

Visual analog scales

Visual analog scale data are presented in Table 2. A significant effect of treatment was found on quality of maintenance of anesthesia ($p = 0.015$), but not on quality of induction of anesthesia ($p = 0.2$) or recovery from anesthesia ($p = 0.447$). The quality of maintenance of anesthesia was significantly greater in DK5IM than in DVK5SC [6 (0–32) mm, $p = 0.024$].

Physiologic variables

Changes in HR over time in the different treatments are presented in Fig. 2a. A significant effect of treatment ($p = 0.005$) and time ($p < 0.001$) but not their interaction ($p = 0.070$) on HR was found. HR was significantly higher in all treatments than in DK5IM [DK5IM *versus* DVK2.5IM: 1.7 (1.2–2.4) beats $minute^{-1}$, $p = 0.003$; DK5IM *versus* DVK5IM: 1.5 (1–2.1) beats $minute^{-1}$, $p = 0.03$; DK5IM *versus* DVK5IV: 1.5 (1–2.1) beats $minute^{-1}$, $p = 0.047$; DK5IM *versus* DVK5SC: 1.5 (1–2.1) beats $minute^{-1}$, $p = 0.041$; DK5IM *versus* DVK10IM: 1.7 (1.2–2.5) beats $minute^{-1}$, $p = 0.002$].

Changes in MAP over time in the different treatments are presented in Fig. 2b. A significant effect of treatment ($p < 0.001$), time ($p < 0.0001$) and their interaction ($p = 0.008$) on MAP was found. MAP was significantly lower in all treatments than in DK5IM [DK5IM *versus* DVK2.5IM: 2.4 (1.3–4.3) mmHg, $p = 0.003$; DK5IM *versus* DVK5IM: 2.8 (1.6–5) mmHg, $p < 0.001$; DK5IM *versus* DVK5IV: 3.1 (1.5–6.2) mmHg, $p = 0.001$; DK5IM *versus* DVK5SC: 3.2 (1.8–5.7) mmHg, $p < 0.0001$; DK5IM *versus* DVK10IM: 1.9 (1.1–3.4) mmHg, $p = 0.021$]. MAP was lower than 70 mmHg in one cat in DK5IM (10 minutes after treatment, 68 mmHg); one cat in DVK5IM (75 minutes after treatment, 64 mmHg); one cat in DVK5IV (baseline, 68 mmHg); and one cat in DVK5SC (30 and 40 minutes after treatment, 69 and 66 mmHg, respectively).

Hemoglobin oxygen saturation data are presented in Table 3. A significant effect of treatment ($p = 0.033$) and time ($p < 0.0001$) but not their interaction ($p = 0.085$) on SpO_2 was found. There was no difference amongst treatment groups when compared with control (DK5IM). SpO_2 was significantly higher than the first measurement from 10 to 65 minutes in DVK2.5IM and from 20 to 65 minutes in DVK5IM. The lowest SpO_2 recorded in the study was in the DVK10IM group at 10 minutes, at 90%.

Respiratory rate data are presented in Table 3. There was a significant time–treatment interaction on f_R ($p = 0.008$) but no effect on treatment ($p = 0.555$) or time alone ($p = 0.523$).

End-tidal carbon dioxide partial pressure data are presented in Table 3. There was a significant treatment ($p = 0.029$) and time effect ($p < 0.0001$) on $P_{E'}CO_2$, but the time–treatment interaction was not significant ($p = 0.5955$). Compared with DK5IM, $P_{E'}CO_2$ was significantly lower in DVK5IM [1.4 (1–1.9), $p = 0.024$] and DVK5IV [1.5 (1.1–2), $p = 0.009$]. For DVK5IV, all $ETCO_2$ measurements from 10 to 120 minutes after injection were significantly lower than baseline (taken as 5 minutes after injection).

Body temperature data are presented in Table 3. A significant time effect ($p < 0.0001$) on body temperature was found, but the treatment effect ($p = 0.068$) and the time–treatment interaction ($p = 0.139$) were not significant. Body temperature was significantly lower than the first measurement from 75 to 140 minutes in DVK5IV.

Discussion

In this study, immobility during noxious stimulation was not observed in all cats at any time point after any treatment. This suggests that at the doses studied, combinations of dexmedetomidine and ketamine, with or without vatinoxan, produce varying levels of sedation but not consistently anesthesia, as immobility during noxious stimulation is considered an essential component of anesthesia (Eger et al. 1997). Overall, vatinoxan significantly attenuated the bradycardia and hypertension observed with dexmedetomidine–ketamine. Increasing doses of ketamine increased the duration of effect.

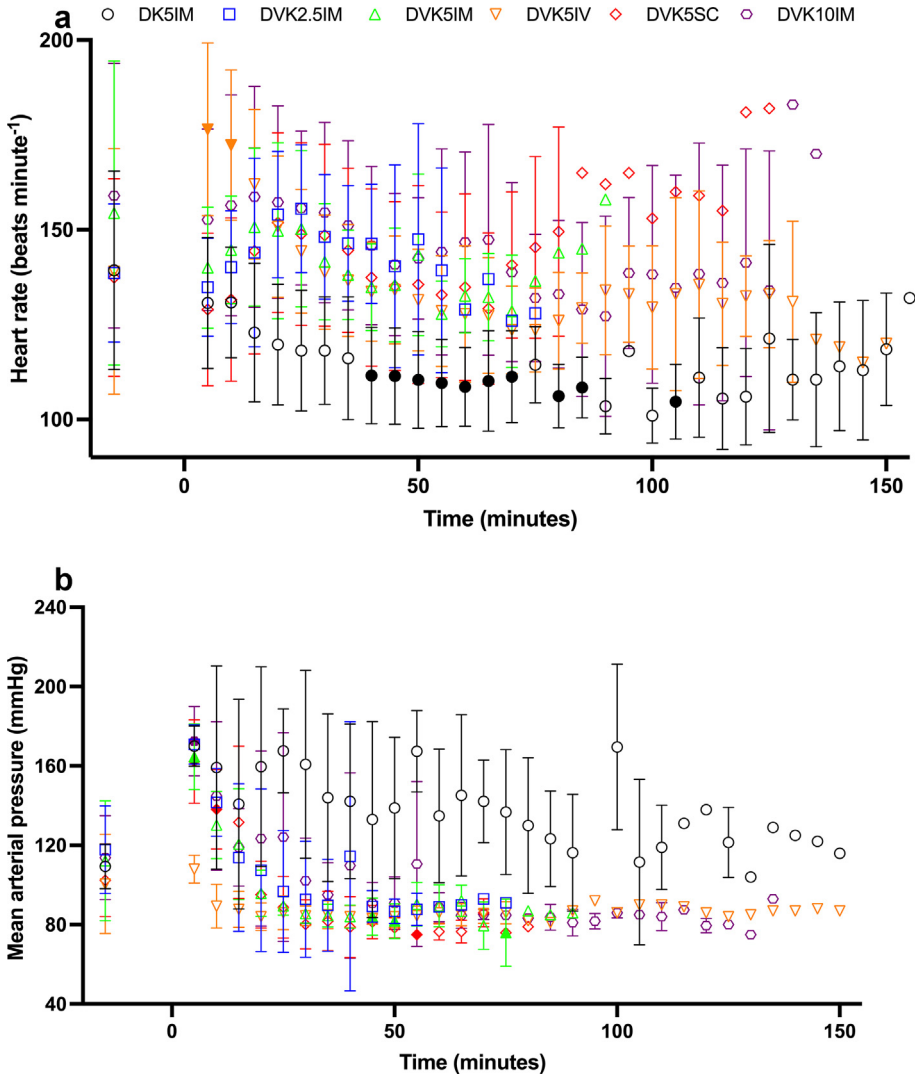

Figure 2 Heart rate (a) and mean arterial pressure (b) over time in cats administered combinations of dexmedetomidine, vatinoxan and ketamine at time 0. D: dexmedetomidine 25 μg kg^{-1}; V: vatinoxan 600 μg kg^{-1}; K2.5: ketamine 2.5 mg kg^{-1}; K5: ketamine 5 mg kg^{-1}; K10: ketamine 10 mg kg^{-1}; IM: intramuscular; IV: intravenous; SC: subcutaneous. Drugs were mixed in the same syringe before injection. A total of six cats were administered DVK5IV and seven cats were administered all other treatments. Heart rate was significantly ($p < 0.05$) higher in all treatments than in DK5IM, and mean arterial pressure was significantly lower in all treatments than in DK5IM. Closed symbols indicate significant ($p < 0.05$) difference from the respective value at baseline (time −15 minutes). Data are mean (symbol) and standard deviation (error bars).

The results of this study should be interpreted in view of several limitations. The sample size was small and power was only determined for one outcome (difference in HR between treatment groups). All other analyses (times, response to electrical stimulation, VAS, MAP, SpO_2, f_R, $P_{E'}CO_2$, body temperature) cannot be easily interpreted and significant differences, where they were found, may not provide a good estimate of the true magnitude of the difference. Equally, where no significant differences were observed, the risk for a type II (false negative) error is unknown, and such errors may have occurred, with failure to identify important differences between treatments. The IV treatment was not randomized but always administered last. This was done because blinding of the observer scoring the quality of induction, maintenance and recovery from anesthesia would have been difficult for this treatment, owing to the almost instantaneous effect and the need for a peripheral IV catheter. Additionally, the IV treatment was primarily included for the pharmacokinetic section of the study (reported separately), and it was considered preferable to prioritize the other treatments in case telemetric transmitters started failing before completion of the study. Although quality of sedation/anesthesia was scored for the IV

Table 3 Mean ± standard deviation (*p*-value for significant differences with the first measurement) hemoglobin oxygen saturation (SpO_2), respiratory rate (f_R), end-tidal partial pressure of carbon dioxide ($P_E'CO_2$) and body temperature (T_{BODY}) following injection of combinations of dexmedetomidine, vatinoxan and ketamine administered at time 0 minute. D, dexmedetomidine 25 μg kg^{-1}; V, vatinoxan 600 μg kg^{-1}; K2.5, ketamine 2.5 mg kg^{-1}; K5, ketamine 5 mg kg^{-1}; K10, ketamine 10 mg kg^{-1}; IM, intramuscular; IV, intravenous; SC, subcutaneous. Drugs were mixed in the same syringe before injection. A total of six cats were administered DVK5IV and seven cats were administered all other treatments. Missing values indicate that the measurement could not be obtained because the cats did not tolerate the sensor (SpO_2), the catheter in their trachea ($P_E'CO_2$) or had recovered from anesthesia (f_R, T_{BODY}) at that time.

Variable	Treatment	Time (minutes)			
		5	10	15	20
SpO_2 (%)	DK5IM		97	98 ± 1	98 ± 3
	DVK2.5IM	97 ± 1	100 ± 1 (<0.001)	99 ± 1 (<0.001)	100 ± 1 (<0.001)
	DVK5IM		98 ± 2	98 ± 2	100 ± 1 (0.01)
	DVK5IV	97 ± 3	98 ± 2	98 ± 2	98 ± 2
	DVK5SC	99	99 ± 2	98 ± 2	99 ± 2
	DVK10IM	100	95 ± 2	96 ± 4	98 ± 3
		25	30	35	40
SpO_2 (%)	DK5IM	97 ± 3	97 ± 2	98 ± 2	100 ± 1
	DVK2.5IM	100 ± 1 (<0.0001)	100 ± 0 (<0.0001)	100 ± 1 (<0.001)	100 ± 1 (<0.001)
	DVK5IM	100 ± 1 (0.004)	100 ± 0 (0.001)	100 ± 0 (0.001)	100 ± 0 (0.001)
	DVK5IV	98 ± 2	98 ± 2	98 ± 1	98 ± 2
	DVK5SC	99 ± 2	98 ± 3	99 ± 1	99 ± 1
	DVK10IM	97 ± 3	98 ± 3	99 ± 2	99 ± 2
		45	50	55	60
SpO_2 (%)	DK5IM	98 ± 1	97 ± 1	98 ± 1	97 ± 1
	DVK2.5IM	99 ± 1 (0.001)	100 ± 0 (<0.001)	100 ± 0 (<0.001)	100 (0.005)
	DVK5IM	100 ± 1 (0.004)	100 ± 0 (<0.001)	100 ± 0 (<0.001)	100 ± 0 (<0.001)
	DVK5IV	98 ± 1	99 ± 1	99 ± 1	99 ± 1
	DVK5SC	99 ± 1	100 ± 0	100 ± 1	99 ± 2
	DVK10IM	99 ± 2	99 ± 2	99 ± 1	99 ± 2
SpO_2 (%)		65	70	75	80
	DK5IM	99 ± 2	99 ± 2	97	98 ± 3
	DVK2.5IM	100 (0.005)			
	DVK5IM	100 ± 0 (0.005)	100	100	100
	DVK5IV	99 ± 1	99 ± 2	99 ± 2	100 ± 1
	DVK5SC	100 ± 1	100	100	100
	DVK10IM	98 ± 2	97 ± 3	98 ± 2	97 ± 2
		85	90	95	100
SpO_2 (%)	DK5IM	98 ± 4	100	100	100
	DVK2.5IM				
	DVK5IM				
	DVK5IV	99	98 ± 2	99 ± 1	99 ± 2
	DVK5SC	100	100	100	100
	DVK10IM	99 ± 1	98 ± 2	99 ± 2	99 ± 2
		105	110	115	120
SpO_2 (%)	DK5IM	97	100		
	DVK2.5IM				
	DVK5IM				
	DVK5IV	99 ± 1	99 ± 0	99 ± 2	98 ± 2
	DVK5SC	100	100		
	DVK10IM	99 ± 2	99 ± 2	98 ± 3	98 ± 3
		125	130	135	140
SpO_2 (%)	DK5IM				
	DVK2.5IM				
	DVK5IM				
	DVK5IV	98 ± 2	98 ± 4	96	96
	DVK5SC				
	DVK10IM	100	99	99	
		145			

(*continued on next page*)

Table 3 (*continued*)

Variable	Treatment	Time (minutes)			
SpO_2 (%)	DK5IM				
	DVK2.5IM				
	DVK5IM				
	DVK5IV	95			
	DVK5SC				
	DVK10IM				
		−15	5	10	15
f_R (breaths minute^{-1})	DK5IM	72 ± 9	38 ± 21	22 ± 14	20 ± 9
	DVK2.5IM	82 ± 39	57 ± 27	40 ± 15	38 ± 15
	DVK5IM	62 ± 20	42 ± 22	27 ± 13	25 ± 10
	DVK5IV	69 ± 24	25 ± 12	21 ± 9	34 ± 12
	DVK5SC	60 ± 13	58 ± 7	42 ± 12	33 ± 10
	DVK10IM	68 ± 35	34 ± 16	22 ± 14	18 ± 9
		20	25	30	35
f_R (breaths minute^{-1})	DK5IM	25 ± 13	28 ± 13	29 ± 14	31 ± 9
	DVK2.5IM	38 ± 9	35 ± 9	38 ± 9	36 ± 11
	DVK5IM	27 ± 11	32 ± 10	30 ± 9	31 ± 6
	DVK5IV	31 ± 11	37 ± 13	38 ± 16	40 ± 9
	DVK5SC	30 ± 13	35 ± 13	33 ± 13	36 ± 9
	DVK10IM	19 ± 8	23 ± 13	23 ± 11	25 ± 10
		40	45	50	55
f_R (breaths minute^{-1})	DK5IM	32 ± 11	36 ± 11	34 ± 11	34 ± 8
	DVK2.5IM	35 ± 7	31 ± 5	38 ± 5	40 ± 3
	DVK5IM	33 ± 9	34 ± 7	37 ± 12	39 ± 6
	DVK5IV	43 ± 15	37 ± 6	32 ± 7	29 ± 6
	DVK5SC	34 ± 10	39 ± 14	36 ± 13	40 ± 13
	DVK10IM	24 ± 7	29 ± 10	30 ± 10	34 ± 9
		60	65	70	75
f_R (breaths minute^{-1})	DK5IM	38 ± 17	40 ± 17	41 ± 13	44 ± 15
	DVK2.5IM	30	36	42	42
	DVK5IM	37 ± 6	41 ± 5	43 ± 9	42 ± 8
	DVK5IV	34 ± 5	39 ± 7	35 ± 3	33 ± 3
	DVK5SC	40 ± 20	43 ± 17	37 ± 12	30 ± 8
	DVK10IM	35 ± 11	30 ± 7	34 ± 9	32 ± 6
		80	85	90	95
f_R (breaths minute^{-1})	DK5IM	43 ± 18	46 ± 20	31 ± 3	30
	DVK2.5IM				
	DVK5IM	30	42	48	
	DVK5IV	40 ± 7	36 ± 6	33 ± 4	37 ± 1
	DVK5SC	31 ± 7	30	30	36
	DVK10IM	30 ± 5	32 ± 5	31 ± 7	38 ± 8
		100	105	110	115
f_R (breaths minute^{-1})	DK5IM	35 ± 11	29 ± 2	31 ± 5	33 ± 4
	DVK2.5IM				
	DVK5IM				
	DVK5IV	34 ± 4	44 ± 3	46 ± 4	41 ± 6
	DVK5SC	36	30	30	30
	DVK10IM	40 ± 3	40 ± 12	35 ± 11	37 ± 16
		120	125	130	135
f_R (breaths minute^{-1})	DK5IM	36 ± 8	36 ± 8	36	42 ± 8
	DVK2.5IM				
	DVK5IM				
	DVK5IV	38 ± 2	36 ± 8	42 ± 8	42
	DVK5SC	60	36		
	DVK10IM	48 ± 0	48	48	54
		140	145	150	155
f_R (breaths minute^{-1})	DK5IM	48 ± 0	42 ± 8	36 ± 0	42
	DVK2.5IM				

Table 3 (*continued*)

Variable	Treatment	Time (minutes)			
	DVK5IM				
	DVK5IV	42	48	42	
	DVK5SC				
	DVK10IM				
		5	10	15	20
$P_{E'}CO_2$ (mmHg)	DK5IM		36	45 ± 8	45 ± 6
	DVK2.5IM		43	43 ± 3	42 ± 2
	DVK5IM		43 ± 5	40 ± 6	40 ± 3
	DVK5IV	54	37 ± 4 (0.004)	37 ± 3 (0.002)	38 ± 4 (0.006)
	DVK5SC			40 ± 4	39 ± 3
	DVK10IM		42 ± 7	44 ± 5	43 ± 4
		25	30	35	40
$P_{E'}CO_2$ (mmHg)	DK5IM	45 ± 6	45 ± 4	42 ± 3	43 ± 2
	DVK2.5IM	40 ± 2	39 ± 3	38 ± 4	38 ± 6
	DVK5IM	38 ± 3	39 ± 3	37 ± 5	39 ± 4
	DVK5IV	38 ± 4 (0.006)	36 ± 4 (0.002)	37 ± 3 (0.003)	35 ± 3 (0.001)
	DVK5SC	41 ± 4	42 ± 3	38 ± 4	42 ± 2
	DVK10IM	42 ± 3	40 ± 3	39 ± 4	40 ± 4
		45	50	55	60
$P_{E'}CO_2$ (mmHg)	DK5IM	41 ± 3	42 ± 2	41 ± 2	42 ± 2
	DVK2.5IM	37 ± 3	39		
	DVK5IM	38 ± 3	37 ± 2	35 ± 3	34 ± 4
	DVK5IV	37 ± 2 (0.005)	36 ± 2 (0.004)	37 ± 2 (0.008)	35 ± 1 (0.003)
	DVK5SC	42 ± 9	40 ± 3	42	42
	DVK10IM	38 ± 4	37 ± 4	38 ± 3	38 ± 3
		65	70	75	80
$P_{E'}CO_2$ (mmHg)	DK5IM	39 ± 3	38 ± 4	37 ± 3	38 ± 4
	DVK2.5IM				
	DVK5IM	33	31	30*	
	DVK5IV	35 ± 2 (0.002)	34 ± 3 (0.001)	36 ± 1 (0.006)	33 (0.003)
	DVK5SC	41	41	38	39
	DVK10IM	38 ± 2	37 ± 4	38 ± 3	38 ± 4
		85	90	95	100
$P_{E'}CO_2$ (mmHg)	DK5IM	38 ± 4	39 ± 2		40
	DVK2.5IM				
	DVK5IM				
	DVK5IV		34 (0.006)	33 (0.003)	32 (0.002)
	DVK5SC				
	DVK10IM	36 ± 4	37 ± 3	35 ± 2	34
		105	110	115	120
$P_{E'}CO_2$ (mmHg)	DK5IM	40	40		
	DVK2.5IM				
	DVK5IM				
	DVK5IV	27 (<0.0001)	30 (<0.001)	30 (<0.001)	31 (<0.001)
	DVK5SC				
	DVK10IM	34	35	36	
		5	10	15	20
$P_{E'}CO_2$ (kPa)	DK5IM		4.8	6 ± 1.1	6 ± 0.8
	DVK2.5IM		5.7	5.7 ± 0.5	5.6 ± 0.3
	DVK5IM		5.8 ± 0.7	5.4 ± 0.8	5.3 ± 0.4
	DVK5IV	7.2	5 ± 0.6 (0.004)	4.9 ± 0.4 (0.002)	5.1 ± 0.5 (0.006)
	DVK5SC			5.3 ± 0.5	5.2 ± 0.4
	DVK10IM		5.6 ± 0.9	5.9 ± 0.7	5.7 ± 0.5
		25	30	35	40
$P_{E'}CO_2$ (kPa)	DK5IM	6 ± 0.9	6 ± 0.5	5.6 ± 0.4	5.7 ± 0.3
	DVK2.5IM	5.4 ± 0.3	5.2 ± 0.4	5 ± 0.5	5 ± 0.8
	DVK5IM	5.1 ± 0.4	5.2 ± 0.4	4.9 ± 0.7	5.1 ± 0.5

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Table 3 (*continued*)

Variable	Treatment	Time (minutes)			
	DVK5IV	5.1 ± 0.5 (0.006)	4.8 ± 0.5 (0.002)	4.9 ± 0.4 (0.003)	4.7 ± 0.3 (0.001)
	DVK5SC	5.5 ± 0.5	5.6 ± 0.4	5.1 ± 0.6	5.5 ± 0.3
	DVK10IM	5.5 ± 0.4	5.3 ± 0.3	5.2 ± 0.6	5.3 ± 0.5
		45	50	55	60
$P_{E'}CO_2$ (kPa)	DK5IM	5.5 ± 0.4	5.6 ± 0.3	5.5 ± 0.2	5.6 ± 0.3
	DVK2.5IM	4.9 ± 0.4	5.2		
	DVK5IM	5.1 ± 0.4	4.9 ± 0.3	4.7 ± 0.4	4.6 ± 0.5
	DVK5IV	4.9 ± 0.2 (0.005)	4.7 ± 0.3 (0.004)	4.9 ± 0.3 (0.008)	4.7 ± 0.2 (0.003)
	DVK5SC	5.5 ± 1.2	5.3 ± 0.4	5.6	5.6
	DVK10IM	5.1 ± 0.6	5 ± 0.5	5 ± 0.3	5 ± 0.4
		65	70	75	80
$P_{E'}CO_2$ (kPa)	DK5IM	5.2 ± 0.4	5.1 ± 0.5	5 ± 0.4	5.1 ± 0.6
	DVK2.5IM				
	DVK5IM	4.4	4.1	4	
	DVK5IV	4.6 ± 0.3 (0.002)	4.5 ± 0.4 (0.001)	4.8 ± 0.2 (0.006)	4.4 (0.003)
	DVK5SC	5.5	5.5	5.1	5.2
	DVK10IM	5.1 ± 0.3	4.9 ± 0.5	5 ± 0.4	5 ± 0.5
		85	90	95	100
$P_{E'}CO_2$ (kPa)	DK5IM	5.1 ± 0.6	5.1 ± 0.3		5.3
	DVK2.5IM				
	DVK5IM				
	DVK5IV		4.5 (0.006)	4.4 (0.003)	4.3 (0.002)
	DVK5SC				
	DVK10IM	4.8 ± 0.5	4.9 ± 0.5	4.6 ± 0.3	4.5
		105	110	115	120
$P_{E'}CO_2$ (kPa)	DK5IM	5.3	5.3		
	DVK2.5IM				
	DVK5IM				
	DVK5IV	3.6 (<0.0001)	4 (<0.001)	4 (<0.001)	4.1 (<0.001)
	DVK5SC				
	DVK10IM	4.5	4.7	4.8	
		5	10	15	20
T_{BODY} (°C)	DK5IM	38.6 ± 0.9	38.7 ± 0.7	38.8 ± 0.8	38.6 ± 0.9
	DVK2.5IM	38.4 ± 0.3	38.7 ± 0.4	38.7 ± 0.4	38.5 ± 0.5
	DVK5IM	38.2 ± 0.3	38.4 ± 0.5	38.4 ± 0.4	38.4 ± 0.4
	DVK5IV	38.1 ± 0.3	38.2 ± 0.3	38.2 ± 0.3	38.4 ± 0.7
	DVK5SC	38.3 ± 0.3	38.3 ± 0.7	38.4 ± 0.6	38.4 ± 0.6
	DVK10IM	38.1 ± 0.1	38.9 ± 0.9	38.9 ± 0.9	38.9 ± 0.9
		25	30	35	40
T_{BODY} (°C)	DK5IM	38.5 ± 0.8	38.7 ± 0.9	38.8 ± 0.8	38.9 ± 0.8
	DVK2.5IM	38.5 ± 0.6	38.7 ± 0.8	38.7 ± 0.9	38.2 ± 0.2
	DVK5IM	38.4 ± 0.5	38.3 ± 0.5	38.2 ± 0.5	38.1 ± 0.5
	DVK5IV	38.1 ± 0.2	38.1 ± 0.3	38 ± 0.2	38 ± 0.2
	DVK5SC	38.2 ± 0.6	38.2 ± 0.6	38 ± 0.7	38 ± 0.6
	DVK10IM	38.8 ± 0.9	38.8 ± 0.9	38.7 ± 0.9	38.6 ± 0.8
		45	50	55	60
T_{BODY} (°C)	DK5IM	38.8 ± 0.8	38.6 ± 0.7	38.6 ± 0.6	38.6 ± 0.6
	DVK2.5IM	38.2 ± 0.2	38.2 ± 0.1	38.4 ± 0.6	38.1
	DVK5IM	38 ± 0.5	37.7 ± 0.4	37.7 ± 0.4	37.7 ± 0.4
	DVK5IV	38 ± 0.2	37.9 ± 0.3	37.8 ± 0.3	37.8 ± 0.3
	DVK5SC	37.9 ± 0.5	37.9 ± 0.5	37.7 ± 0.3	37.6 ± 0.4
	DVK10IM	38.6 ± 0.9	38.5 ± 0.9	38.4 ± 0.8	38.2 ± 0.6
		65	70	75	80
T_{BODY} (°C)	DK5IM	38.5 ± 0.6	38.5 ± 0.5	38.7 ± 0.6	38.3 ± 0.4
	DVK2.5IM	38.1			
	DVK5IM	37.7 ± 0.3	37.4	37.4	37.3
	DVK5IV	37.7 ± 0.2	37.6 ± 0.1	37.5 ± 0.1 (0.009)	37.5 ± 0.1 (0.031)
	DVK5SC	37.4 ± 0.5	37.2 ± 0.6	37.6	37.6

Table 3 (*continued*)

Variable	Treatment	Time (minutes)			
	DVK10IM	38.2 ± 0.6	38.1 ± 0.6	38.1 ± 0.6	37.9 ± 0.5
		85	90	95	100
T_{BODY} (°C)	DK5IM	38.1 ± 0	38.1 ± 0	38.1	38.1 ± 0
	DVK2.5IM				
	DVK5IM				
	DVK5IV	37.4 ± 0.1 (0.047)	37.3 ± 0.1 (0.007)	37.3 ± 0.1 (0.013)	37.3 ± 0.1 (0.013)
	DVK5SC	37.5	37.5	37.4	37.3
	DVK10IM	37.8 ± 0.3	37.8 ± 0.4	37.7 ± 0.3	37.7 ± 0.3
		105	110	115	120
T_{BODY} (°C)	DK5IM	38.1 ± 0.1	38.1 ± 0.1	38	38
	DVK2.5IM				
	DVK5IM				
	DVK5IV	37.2 ± 0.1 (0.002)	37.1 ± 0.1 (<0.001)	37.1 ± 0 (<0.001)	37.1 ± 0 (<0.001)
	DVK5SC	37.2	37.2	37.2	
	DVK10IM	37.7 ± 0.3	37.6 ± 0.2	37.4 ± 0.2	37.4 ± 0.2
		125	130	135	140
T_{BODY} (°C)	DK5IM	38	37.9	37.9	
	DVK2.5IM				
	DVK5IM				
	DVK5IV	37 ± 0 (<0.001)	37 (0.009)	37 (0.009)	37 (0.009)
	DVK5SC				
	DVK10IM	37.4	37.4	37.4	

treatment, data were not included in the analysis because of their subjective nature and the lack of blinding. On most study days, data were collected simultaneously from two cats. This necessitated the use of different pulse oximeters and capnographs. This can potentially introduce discrepancies in these measurements. Arterial blood pressure was not available for all cats in all treatments as the telemetric transmitters sometimes failed to provide measurements. The subjects of this study were all young, clinically healthy male neutered cats. This does not represent the variability in the general cat population and it is unknown how sex, age or systemic disease would have affected the outcomes.

Vatinoxan has been shown to increase the rate of absorption of drugs coadministered IM in a previous study in dogs (Kallio-Kujala et al. 2018). In the study reported here, the addition of vatinoxan to a dexmedetomidine–ketamine combination did not produce a significant difference in time to recumbency and immobility. Recumbency and immobility were achieved more slowly after SC than after IV drug administration. Nevertheless, the onset of sedation/anesthesia, as characterized by recumbency and immobility, was rapid with all treatments, with recumbency achieved within 5 minutes and immobility within 10 minutes in most cats.

The addition of vatinoxan to dexmedetomidine–ketamine combinations significantly reduced the time for initial (head lift, sternal recumbency) but not total (walking) recovery. This is most likely owing to the reduced vasoconstriction and increased cardiac output produced by the addition of vatinoxan, resulting in increased rate of dexmedetomidine elimination and increased volume of distribution, reducing the plasma and effect site concentrations (Honkavaara et al. 2012; Pypendop et al. 2016, 2017). A shortening of dexmedetomidine–ketamine anesthesia time by vatinoxan has been shown in dogs (Turunen et al. 2020). The lack of statistical significance on time to walking may be related to insufficient statistical power as mean time to walking following DK5IM and DVK5IM differed by more than 1 hour.

No treatment produced immobility during noxious stimulation in all cats. This suggests that at the dose studied, the combinations produce sedation, but that anesthesia (as characterized by lack of movement in response to noxious stimulation) is not produced consistently. In addition, no cat in the SC treatment was immobile during noxious stimulation at any time point. Moreover, the subjective quality of maintenance of sedation/anesthesia was significantly worse in the SC treatment, confirming that although SC administration was effective at producing recumbency and immobility in the absence of stimulation, the effects were inferior to those following IM administration. The reasons for the lack of consistency in producing immobility are unclear. The dose of dexmedetomidine used had been previously shown to result in profound sedation when combined with the dose of vatinoxan used (Honkavaara et al. 2017b). The doses of ketamine were selected to represent the range of doses used in previous studies on medetomidine or dexmedetomidine–ketamine combinations to perform castration, ovariectomy or ovariohysterectomy in cats (Joyce & Yates 2011; Ko et al. 2011; Fernandez-Parra et al. 2017; Khenissi et al. 2017; Diep et al.

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2020; Posner et al. 2020; Gomes et al. 2022a,b; Rufiange et al. 2022; Malo et al. 2023). Comparisons of the results in the present study with these previously published studies are complicated because some used higher doses of dexmedetomidine but with doses of ketamine lower than the highest dose in this study, some used lower doses of both dexmedetomidine and ketamine, and all studies used additional drugs or techniques (opioids, midazolam, local anesthesia). Because when used in combination, both dexmedetomidine and ketamine contribute to producing anesthesia, it is anticipated that a lower dose of one of the drugs could be compensated for by a higher dose of the other drug. None of the previous studies included vatinoxan, and it is possible that this agent decreases the potency of the dexmedetomidine and ketamine combination. Vatinoxan has been shown to decrease the potency of dexmedetomidine as an adjunct to inhalant anesthesia in dogs and cats (Pypendop et al. 2019; Hector et al. 2021). Lastly, it is possible that the noxious stimulus used in this study elicited a stronger response than surgery. Indeed, the stimulus was expected to be maximally noxious (Eger et al. 1965), whereas surgery may not produce maximal nociception.

The inclusion of vatinoxan significantly attenuated the decrease in HR observed in the dexmedetomidine–ketamine treatment. Dexmedetomidine decreases HR via alpha-2 adrenoceptor-mediated vasoconstriction resulting in a baroreceptor-mediated increase in vagal tone (Murrell & Hellebrekers 2005). Effects on alpha-2 adrenoceptors within the CNS may contribute to the decrease in HR. Dexmedetomidine–ketamine combination administered to cats has been previously shown to significantly decrease HR (Selmi et al. 2003), similar to our study. The attenuation of the bradycardic effect of dexmedetomidine in the treatments including vatinoxan is similar to previous studies performed in cats but without ketamine (Honkavaara et al. 2017a,b). Vatinoxan antagonizes the effects of dexmedetomidine outside of the CNS, including the vasoconstrictive effect, preventing the baroreceptor activation and therefore the bradycardia. This is further illustrated by the difference in MAP with and without vatinoxan in this study. Following intramuscular IM administration, the initial vasoconstrictive effect of dexmedetomidine may still be present but disappears quickly (Siao et al. 2017). This is in agreement with the effects on MAP observed in this study.

Although statistically significant effects were found on SpO_2, f_R and $P_E'CO_2$, the effects are considered to be clinically insignificant. SpO_2 was low in some cats; this may be owing to the dexmedetomidine-induced vasoconstriction at the early time points resulting in erroneous measurements (Sinex 1999). Nevertheless, delivery of oxygen via a facemask may increase patient safety when dexmedetomidine–ketamine combination with or without vatinoxan are used.

Body temperature decreased over time, without significance differences between treatments. This is likely because of the decrease in heat production as a result of decreased muscle activity and the effect of dexmedetomidine on the thermoregulatory center (Sessler 2009).

Conclusion

In healthy cats, the addition of vatinoxan (600 μg kg^{-1}) to dexmedetomidine (25 μg kg^{-1}) and ketamine (5 mg kg^{-1}) reduced bradycardia. At the doses used, dexmedetomidine–ketamine combinations with or without vatinoxan did not consistently produce immobility in response to noxious stimulation. The effects following SC administration were inferior to those following IM administration. The dose of ketamine influenced the duration of effect. Dexmedetomidine–vatinoxan–ketamine combinations, at the doses studied, may be useful to produce sedation for non-painful procedures.

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Authors' contributions

YHL: data acquisition, data interpretation, manuscript preparation. BHP: study design, data acquisition, data analysis, data interpretation, manuscript preparation. JH and LSB: study design, manuscript preparation.

Conflict of interest statement

Vatinoxan was provided free of charge by Vetcare Ltd. JH received financial support from Vetcare Ltd. in the past. The other authors declare no conflict of interest.

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Supporting information

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Appendix SA. Telemetric transmitter implantation and *P* values.

