https://doi.org/10.17221/138/2020-VETMED

Effects of dexmedetomidine or tramadol continuous rate infusions on the propofol requirements and cardiorespiratory variables in propofol-ketamine-midazolam anaesthetised cats

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Citation: Souza T, Anjos N, Kersul I, Martins Filho E, Nunes T, Barbosa V (2022): Effects of dexmedetomidine or tramadol continuous rate infusions on the propofol requirements and cardiorespiratory variables in propofol-ketamine-midazolam anaesthetised cats. Vet Med-Czech 67, 199–205.

Abstract: The aim of this study was to compare the effects of midazolam-ketamine alone or in combination with dexmedetomidine or tramadol in a constant rate infusion (CRI) on the minimum infusion rate (MIR) of propofol and the cardiorespiratory function in cats undergoing an ovariohysterectomy (OH). This was a prospective, randomised, blinded clinical study. Twenty-four healthy female mixed-breed cats were premedicated with ketamine and midazolam. Propofol was used for the induction and maintenance of the anaesthesia (starting at 18 mg/kg/h). Cats were assigned to groups (*n* = 8) to receive one of the following intravenous treatments: midazolam-ketamine group (MKG; ketamine 0.6 mg/kg/h); midazolam-ketamine-dexmedetomidine group [MKDG; ketamine 0.6 mg/kg/h and dexmedetomidine loading dose (LD) 1 mg/kg, CRI 1 mg/kg/h)] or midazolam-ketamine-tramadol group [MKTG; ketamine 0.6 mg/kg/h and tramadol (LD 2 mg/kg, CRI 1 mg/kg/h)]. During the OH, the propofol infusion was adjusted based on the clinical signs to maintain adequate anaesthetic depth. Selected variables were measured before (T0) and after (T1) the anaesthesia induction and during six surgical time points (T2–T7). The mean arterial pressure was higher and the heart rate was lower in MKDG at T1 (than in MKG and MKTG). The mean ± SD MIR of propofol were 17.4 ± 3.2, 15.0 ± 2.8 and 12.6 ± 3.5 mg/kg/h for MKG, MKTG, and MKDG, respectively. We conclude that, compared to midazolam-ketamine alone, midazolam-ketamine-tramadol and midazolam-ketamine-dexmedetomidine reduced the MRI of propofol by 13.8% and 27.5%, respectively, without significant changes in the selected indicators.

Keywords: alpha-2 agonist; anaesthetic-sparing effect; feline; total intravenous anaesthesia

Total intravenous anaesthesia (TIVA) is becoming a vital technique for general anaesthesia and a well-established anaesthetic concept for small animals (Raffe 2020). The choice of drugs should provide cardiorespiratory stability, satisfactory management of the perioperative pain, and good quality of the recovery (Ilkiw et al. 2003). A balanced anaesthetic approach may produce better results than

https://doi.org/10.17221/138/2020-VETMED

using a single agent because each drug acts a different part of the pain pathway (Souza et al. 2010; Mannarino et al. 2012; Ravasio et al. 2012).

Propofol is an anaesthetic agent with rapid onset, distribution, and elimination after intravenous (i.v.) administration. However, it requires high doses as a sole anaesthetic agent, inducing adverse effects such as myocardial depression, metabolic acidosis, impaired platelet aggregation, and extended recovery (Kang et al. 2012). Ketamine, a dissociative anaesthetic, is being re-evaluated as an analgesic drug with haemodynamic effects considered opposite and complementary to those of propofol. These haemodynamic effects include increased myocardial contractility and peripheral vascular resistance, which, in turn, causes an increase in mean arterial pressure (MAP) and heart rate (HR) (Ilkiw et al. 2003; Ambros and Duke 2013). In cats, the combination of ketamine and propofol (ketofol) provides a good and adequate anaesthesia and postoperative analgesia with rapid and smooth recovery without any adverse effects. This anaesthetic protocol may be considered adequate for a brief and moderately painful surgery, even in a species such as cats, which possess peculiar metabolic characteristics (Ravasio et al. 2012; Zonca et al. 2012).

Dexmedetomidine is an alpha-2-agonist characterised by high specificity for alpha-2 receptors and has pronounced sedative and hypnotic effects, potentiating anaesthetic agents (Carollo et al. 2008; Souza et al. 2010). A low dose of a dexmedetomidine constant rate infusion (CRI) (0.5 mg/kg/h) reduces the isoflurane requirements for the maintenance of anaesthesia with minimal effects on the HR in cats undergoing an ovariohysterectomy (Simon et al. 2018). Tramadol is a synthetic codeine analogue whose analgesic effects result from complex interactions with opiate receptors and activation of the descending inhibitory pathways. In cats undergoing a gonadectomy, tramadol, at a dose of 2 mg/kg intravenously (i.v.), does not produce any evident intraoperative cardiorespiratory side effects (Cagnardi et al. 2011). In addition, the oral administration of tramadol (8.6 mg/kg to 11.6 mg/kg) in cats has been shown to significantly reduce the minimum alveolar concentration (MAC) of sevoflurane (1.48 ± 0.20%) compared to a placebo (2.45 ± 0.22%) (Ko et al. 2008). Based on experience with other species in which the benefits of balanced intravenous anaesthesia are reported to reduce the anaesthetic consumption with an increase in safety, we suppose a similar pattern of response in cats undergoing different CRIs.

The aim of this study was to compare the effects of a CRI of ketamine, alone or in combination with dexmedetomidine or tramadol, on the propofol requirement and subsequent cardiorespiratory variables in cats undergoing an ovariohysterectomy.

MATERIAL AND METHODS

We included twenty-four client owned female mixed-breed cats (mean age, 1.9 ± 0.8 years; mean body weight, 3.0 ± 0.6 kg), which were considered to be healthy on the basis of the medical history, physical examination, complete blood count, and serum biochemical analyses. Each cat was randomised using an Excel software program random number generator into one of three treatment groups (n = 8): the midazolam-ketamine group (MKG), the midazolam-ketamine-dexmedetomidine group (MKDG), and the midazolam-ketamine-tramadol group (MKTG). The study was approved by the Ethics Committee of the School of Veterinary Medicine and Animal Science at the Federal University of Bahia under Protocol No. 49/2017.

All the cats were anaesthetised with 3.0 mg/kg of ketamine (Cristália, São Paulo, SP, Brazil) and 0.2 mg/kg of midazolam (Cristália, São Paulo, SP, Brazil) intramuscularly (i.m.). Sequentially, a catheter (Becton-Dickinson, Juiz de Fora, MG, Brazil) was inserted in the left cephalic vein and sodium cephalothin (30 mg/kg) (ABL, Cosmópolis, SP, Brazil) and meloxicam (0.1 mg/kg) (Ourofino, SP, Brazil) were administered (i.v.). In all the protocols, 10 min after the ketamine-midazolam administration, propofol (6.0 mg/kg) (Cristália, São Paulo, SP, Brazil) was used for the anaesthesia induction (over 45–60 s to sedate the patient). After intubation, the cats were placed in dorsal recumbency on electrical thermal mattresses and connected to a non-rebreathing anaesthesia system with a fresh gas flow of 500 ml/kg/min (FiO_2 = 1.0). Immediately after the anaesthesia induction in MKG, a CRI of propofol (starting at 18 mg/kg/h) and ketamine (0.6 mg/kg/h) was started. The cats in the MKDG and MKTG groups received similar treatment; however, in combination with ketamine, the MKDG group received a loading dose (LD) of dexmedetomidine (1 mg/kg) (Zoetis, Campinas, SP, Brazil), followed by a CRI of the

https://doi.org/10.17221/138/2020-VETMED

same drug (1 mg/kg/h), and the MKTG group received an LD of tramadol (2 mg/kg) (Pfizer, São Paulo, SP, Brazil), followed by a CRI of the same drug (1 mg/kg/h). The loading doses were manually administered i.v., after the anaesthesia induction, over a period of 60 seconds. Ten minutes after the anaesthesia induction, when signs of adequate anaesthetic depth appeared (rotated globe, absence of lateral palpebral reflex, absence of or reduced medial palpebral reflex, and absence of jaw tone), the ovariohysterectomy was performed. The following selected variables were measured and recorded using a multiparameter monitor (Digicare Animal Health, FL, USA): heart rate (HR), obtained using 3-lead electrocardiography; respiratory rate (*f*R), measured by capnography always in the presence of a regular respiratory rhythm with no artifact on the capnograms; end-tidal carbon dioxide partial pressure ($EtCO_2$), measured via the mainstream technique; oxygen saturation of haemoglobin (SpO_2), obtained using a probe placed on the tongue; MAP, noninvasively monitored using oscillometry and a cuff with a width approximately 40% of the circumference of the limb, placed on the right thoracic limb; and rectal temperature (RT), monitored using an electronic probe placed into the rectum. These variables were measured 10 min after the premedication and immediately prior to the anaesthesia induction (T0); 10 min after the anaesthesia induction (T1); at the end of the celiotomy (T2); after clamping of the right ovarian pedicle (T3), left ovarian pedicle (T4), and uterine cervix (T5); and at the end of suture placement in the abdominal muscles (T6) and skin (T7); however, the $EtCO_2$ and SpO_2 were not measured at T0.

The propofol CRI was altered during the protocol, aiming to maintain an anaesthetic plane sufficient to inhibit a response to the pain stimuli, based on ocular globe evaluation: 1 – insufficient (centralised globe and presence of palpebral reflexes); 2 – dequate (rotated globe, absence of lateral palpebral reflex, and absence of or reduced medial palpebral reflex); or 3 – deep (centralised globe and absence of palpebral reflexes) [adapted from Comassetto et al. (2015)]. Variations in the cardiorespiratory parameters were also considered, so that in the absence of an autonomic response with the animal in an adequate or deep anaesthetic plane as based on the ocular globe evaluation – characterised by the absence of changes in *f*R, HR, and MAP or by a 20% reduction in at least two variables (compared with T1) – the propofol CRI was decreased by 3 mg/kg/h. When we observed a 20% increase in at least two of these variables (compared with T1) associated with the insufficient anaesthetic plane, the propofol CRI was increased by 3 mg/kg/h. When there was a divergence between the ocular evaluation and the cardiorespiratory variables, the change in propofol CRI was based only on a simultaneous and similar variation in two of these physiological parameters: *f*R, HR, or MAP (Ravasio et al. 2012; Comassetto et al. 2015). Changes in the propofol CRI, when necessary, were made only at the time of surgical nociceptive stimulus (T2, T3, T4, T5, T6, and T7). After any dose change, the propofol infusion was maintained at the same rate for 10 min before further adjustment. The minimum infusion rate (MRI) of propofol was determined for each cat to provide a single data point. The mean of these values was then determined to provide the infusion rate for patients receiving ketamine-dexmedetomidine, ketamine-tramadol, and those receiving only ketamine.

GraphPad Prism v6 (GraphPad Software, CA, USA; www.graphpad.com) was used for the statistical analysis. The data normality was assessed using the Shapiro-Wilk test. The parametric variables were subjected to a repeated-measures analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. For comparison among the groups at each time point, a one-way ANOVA, followed by Tukey's multiple comparison test, was used. The nonparametric variables were subjected to Friedman's nonparametric test for comparison among moments, followed by Dunn's multiple comparison test. For comparison among the treatments, the Kruskal-Wallis test was used, followed by Dunn's multiple comparison test. The statistical significance was indicated by $P < 0.05$.

RESULTS

Surgery was performed without complications in all the cases, and all the cats were discharged from the hospital the same day after complete recovery. There were no differences ($P > 0.05$) in the age or weight of the animals or in the duration of the ovariohysterectomy [MKG, 60 min (45–80 min); MKDG, 58 min (45–75 min); and MKTG, 60 min (46–77 min)]. The HR, MAP, *f*R, SpO_2, $EtCO_2$, and RT in all three groups are shown in Table 1. After

https://doi.org/10.17221/138/2020-VETMED

Table 1. Physiological parameters in cats anaesthetised with propofol-ketamine-midazolam receiving a ketamine (MKG), ketamine-dexmedetomidine (MKDG) or ketamine-tramadol (MKTG) constant rate infusion. Data are represented as a mean ± SD

Variable	Group	Time points							
		T0	T1	T2	T3	T4	T5	T6	T7
HR (beats/minute)	MKG	194 ± 22	177 ± 18^{A*}	166 ± 14*	168 ± 30*	169 ± 22*	170 ± 20*	174 ± 20	170 ± 9*
	MKDG	192 ± 15	162 ± 10^{B*}	151 ± 20*	163 ± 15*	175 ± 19	164 ± 19*	166 ± 16*	159 ± 12*
	MKTG	200 ± 5	183 ± 27^{A*}	163 ± 29*	156 ± 32*	180 ± 40*	179 ± 35*	173 ± 27*	168 ± 32*
MAP (mmHg)	MKG	112 ± 24	101 ± 11^{A*}	103 ± 33	135 ± 15	133 ± 19	128 ± 24	119 ± 27	107 ± 27
	MKDG	101 ± 14	126 ± 13^{B}	100 ± 12	118 ± 24	117 ± 23	102 ± 27	119 ± 29	105 ± 24
	MKTG	113 ± 22	103 ± 7^{A*}	91 ± 20	106 ± 26	113 ± 24	105 ± 26	125 ± 13	112 ± 14
f_R (breaths/minute)	MKG	35 ± 9	15 ± 6*	14 ± 6*	16 ± 5*	13 ± 5*	9 ± 1^{A*}	9 ± 2*	11 ± 5*
	MKDG	37 ± 8	15 ± 7*	16 ± 6*	18 ± 9*	18 ± 9*	15 ± 6^{B*}	15 ± 6*	16 ± 7*
	MKTG	35 ± 8	20 ± 5*	13 ± 7*	12 ± 5*	10 ± 2*	13 ± 5*	13 ± 6*	13 ± 5*
SpO_2 (%)	MKG	–	100 ± 2	100 ± 1	99 ± 1	99 ± 1	100 ± 1	99 ± 1	100 ± 1
	MKDG	–	100 ± 1	100 ± 3	98 ± 3	98 ± 1	98 ± 1	99 ± 2	97 ± 2
	MKTG	–	96 ± 3	99 ± 1	98 ± 1	99 ± 1	98 ± 1	99 ± 1	99 ± 1
$EtCO_2$ (mmHg)	MKG	–	36 ± 5	41 ± 3	38 ± 4	40 ± 2	43 ± 5	41 ± 4	44 ± 6
	MKDG	–	43 ± 8	48 ± 4	43 ± 6	42 ± 8	42 ± 7	42 ± 8	40 ± 5
	MKTG	–	40 ± 7	47 ± 5	44 ± 7	42 ± 7	43 ± 7	44 ± 9	42 ± 6
RT	MKG	38.2 ± 0.4	38.2 ± 0.4	38 ± 0.3*	37.9 ± 0.4*	37.8 ± 0.3*	37.6 ± 0.3*	37.4 ± 0.1^{A*}	37.4 ± 0.3*
	MKDG	38.2 ± 0.3	38.2 ± 0.3	38 ± 0.2	38 ± 0.2	37.8 ± 0.2	37.6 ± 0.3*	37.6 ± 0.2*	37.5 ± 0.2*
	MKTG	38.2 ± 0.3	38.2 ± 0.3	38.1 ± 0.3	38 ± 0.2	37.9 ± 0.3	37.8 ± 0.3*	37.8 ± 0.2^{B*}	37.5 ± 0.2*

*Significantly ($P < 0.05$) different from the values at the initial time-point (T0) within each group; ^{A,B}Statistically significant differences between the groups within each time-point in the same physiological parameter

$EtCO_2$ = end-tidal carbon dioxide partial pressure; fR = respiratory rate; HR = heart rate; MAP = mean arterial pressure; RT = rectal temperature; SpO_2 = pulse oximetry

anaesthesia induction, a significantly lower HR was observed in MKDG ($P = 0.003\,1$) and MAP was significantly higher in MKDG ($P = 0.02$) than in MKG and MKTG. At the same time point (T1), the MAP decreased in MKG and MKTG compared with that at the first evaluation time point (T0), and the HR decreased in all the groups until the last time point (T7). The fR decreased significantly throughout the anaesthetic period compared to the initial means for all the treatments. A significantly lower fR was observed after clamping the uterine cervix in cats treated with ketamine alone ($P = 0.028\,9$). There were no significant differences ($P > 0.05$) between the groups in the end-tidal carbon dioxide partial pressure and oxygen saturation. The RT decreased throughout the infusion period, and a significant difference in the RT was observed between MKG and MKTG ($P = 0.005$) after the end of the suture placement in the abdominal muscles.

The MRI of propofol was significantly lower in the MKTG ($P = 0.006$) and MKDG ($P = 0.003$) groups than in the MKG group, with the mean values for MKG, MKTG, and MKDG being 17.4 ± 3.2, 15.0 ± 2.8 and 12.6 ± 3.5 mg/kg/h, respectively.

DISCUSSION

The use of TIVA in animals has become a popular technique for the induction and maintenance of anaesthesia following the introduction of more elaborate delivery systems and newer short-acting drugs. In this study, the cardiorespiratory indicators were within the clinically acceptable ranges in all three groups. The decrease in the HR with all the treatments from T1 (10 min after anaesthesia induction) probably occurred due to the central sympatholytic and cardiovascular depression action of propofol

https://doi.org/10.17221/138/2020-VETMED

(Mannarino et al. 2012). However, the HR at T1 was lower in the MKDG group than in the other two groups. One of the effects of dexmedetomidine on the cardiovascular system is the reduction in the HR, mediated centrally in the reflex response to the initial hypertension, in addition to the recognised sympatholytic activity (Carollo et al. 2008; Farag et al. 2012). However, there were no values below normality (100–200 beats per min) or rhythm alterations, such as atrioventricular blocks (Mathis 2016), as reported by others (Souza et al. 2010; Pypendop et al. 2011; Ravasio et al. 2012).

An increase in the MAP was observed only in the dexmedetomidine-treated group after the anaesthesia induction. In animals, the predominant effects of dexmedetomidine on the vascular resistance are due to the central noradrenergic and peripheral vasoconstrictive activities, demonstrating an increase in the perfusion potential associated with the effect of this alpha-2 agonist (Ravasio et al. 2012). Notably, to date, the late hypotensive effects typical of the central interaction with alpha-2 receptors have not been detected (Carollo et al. 2008; Farag et al. 2012). In contrast, at the same time point, there was a decrease in the arterial pressure in MKG and MKTG. A reduction in sympathetic tone, peripheral vasodilation, negative inotropic and chronotropic actions, and baroreceptor reflex depression are the main factors responsible for the decrease in the arterial pressure after propofol administration (Yang et al. 1997). However, in both the MKG and MKTG groups, the means were restored sequentially.

The elevated *f*R, probably due to the stress associated with the previous containment and venepuncture of the animals at T0, reduced T1 onwards to physiological levels (8–20 bpm) in the different groups, demonstrating the stability provided by the anaesthetic protocols. At T5, lower mean *f*R values were detected in the MKG group than in the MKDG group, probably because of the higher propofol infusion rates required to maintain the surgical anaesthetic depth in the former, once the respiratory depressant characteristics of propofol have been well established (Oliveira et al. 2018).

The $EtCO_2$ data confirmed the respiratory stability without interference by the treatments in question (Table 1). However, at T2, the mean $EtCO_2$ values in the MKTG and MKDG groups were above the reference levels (35–45 mmHg), suggesting that the tramadol and dexmedetomidine LDs potentiated the depressant effects of propofol. High blood CO_2 concentrations persist when high rates of dexmedetomidine are used during target-controlled infusion in cats anaesthetised with isoflurane (Pypendop et al. 2011). In addition, the use of tramadol (2 mg/kg i.m.) in cats anaesthetised with sevoflurane results in a decrease in the *f*R and an increase in the arterial CO_2 blood levels, without any clinical significance (De Lacerda et al. 2016). The stability of SpO_2 discards any possible hypoxemic events arising from the different treatments, a finding also observed in cats treated with the ketofol combination with or without dexmedetomidine (Ravasio et al. 2012), as well as in cats treated with tramadol during anaesthesia with sevoflurane (De Lacerda et al. 2016). No episodes of hypothermia were detected, despite the small decrease in temperature over time in all the groups.

The inclusion of tramadol and dexmedetomidine significantly reduced the propofol-ketamine CRI by 13.8 and 27.5%, respectively. Notably, the limitation of the present study is the lack of literature that elucidate pharmacokinetic studies on the CRI of tramadol in cats. The CRI used was estimated based on canine studies (Mahidol et al. 2015; Thengchaisri and Mahidol 2019), considering the metabolic characteristics registered with the use of tramadol (bolus) in cats (Pypendop and Ilkiw 2008) and the absence of adverse effects typical of an overdose. Although no studies on the CRI of tramadol in cats have been conducted, in dogs, the comparison of tramadol (1.5 mg/kg LD and CRI 2.6 mg/kg/h) and tramadol-lidocaine (tramadol CRI 2.6 mg/kg/h; and lidocaine 1.0 mg/kg LD and CRI 6 mg/kg/h) results in a MAC-sparing effect of tramadol-lidocaine greater than that of tramadol alone (8.2 ± 8.9% vs. 30.1 ± 10.7%) (Thengchaisri and Mahidol 2019). Similar isoflurane-sparing effects are registered using a CRI of morphine alone (25 ± 6%) or morphine-tramadol (39 ± 9%) in dogs (Mahidol et al. 2015). Therefore, pharmacokinetic studies are needed to clarify whether a higher CRI of tramadol would result in more important anaesthetic-sparing effects and whether they would be safe for domestic cats. In contrast, the use of dexmedetomidine in a single dose or CRI has been widely reported in cats (Souza et al. 2010; Pypendop et al. 2011; Ravasio et al. 2012; Simon et al. 2018; Raffe 2020). Dexmedetomidine (0.5 mg/kg LD and CRI 0.5 mg/kg/h) reduces the overall isoflurane requirements to maintain the anaesthesia by 21%

https://doi.org/10.17221/138/2020-VETMED

in cats undergoing an ovariohysterectomy (Simon et al. 2018). In cats sedated with dexmedetomidine (4 mg/kg), an epidural anaesthesia with lidocaine (1 mg/kg) associated with the CRI of dexmedetomidine (15 mg/kg/h) significantly decreased isoflurane consumption and resulted in a better quality but longer duration recovery in relation to the use of epidural lidocaine or epidural lidocaine-dexmedetomidine (2 mg/kg) (Souza et al. 2010). It is important to emphasise that these authors used a CRI of dexmedetomidine 15 times higher than what we used in the present study and, despite this, they considered this alpha-2 agonist safe for balanced anaesthesia in healthy cats.

In conclusion, the results of our study confirmed that dexmedetomidine can reduce the propofol requirements to a higher degree than tramadol in propofol-ketamine-midazolam anaesthetised cats. In all the treatments, no significant changes in the selected indicators were detected.

Acknowledgement

The authors would like to thank FAPESB/Brazil for the assistantship of Thamires Barreto Souza. The authors also wish to thank E. F. Martins Filho for performing the statistical analyses (in memoriam).

Conflict of interest

The authors declare no conflict of interest.

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Received: June 29, 2020
Accepted: December 29, 2021
Published online: February 14, 2022