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A clinical comparison of remifentanil or alfentanil in propofol-anesthetized cats undergoing ovariohysterectomy

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Sixteen cats were used to compare the cardiovascular and anesthetic effects of remifentanil (REMI) or alfentanil (ALF) in propofol-anesthetized cats undergoing ovariohysterectomy. After premedication with acepromazine, anesthesia was induced and maintained with a constant rate infusion of propofol (0.3 mg/kg/min). REMI or ALF infusions were administered simultaneously with propofol. Heart rate (HR), systolic arterial pressure (SAP), pulse oximetry (SpO_2), rectal temperature (RT), and response to surgical stimulation were recorded at predefined time points during anesthesia. Data [mean ± standard deviation (SD)] were analyzed by analysis of variance (ANOVA) for repeated measures followed by a Dunnett's test and Student *t*-test ($P < 0.05$). SAP was significantly lower in ALF group than in REMI group. Extubation time was significantly shorter in REMI than in ALF group. Overall infusion rate of REMI and ALF was 0.24 ± 0.05 μg/kg/min and 0.97 ± 0.22 μg/kg/min, respectively. The combination of propofol and REMI or ALF provided satisfactory anesthesia in cats undergoing ovariohysterectomy.

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Inhalant anesthetics are commonly used for maintenance of anesthesia in clinical practice. However, these drugs produce dose-dependent cardiorespiratory depression[1] and are not suitable for procedures that involve the airways, such as some of the dental surgeries, airway exams, bronchoalveolar lavage and bronchoscopy.[2] Inhalant anesthesia is also dependent on expensive equipment and operating-room personnel may be exposed to low concentrations of anesthetic gases during vaporizer filling or from leaks in the patient breathing circuit. Total intravenous anesthesia (TIVA) is a popular technique in humans after the development of drugs such as propofol and short-acting opioids, as well as improved infusion systems.[3] In injured cats, the combination of propofol and fentanyl resulted in better cardiovascular stability when compared with isoflurane and fentanyl.[1]

Propofol is a highly lipophilic anesthetic agent characterized by rapid onset, distribution and elimination phases after intravenous (IV) administration, however, high doses that are required to attenuate autonomic responses to noxious stimuli are also associated with marked cardiorespiratory depression.[4] The use of potent, rapid and ultra-short-acting opioid analgesics has been shown to decrease propofol requirements for maintenance of anesthesia.[3] In cats, the combination of propofol and fentanyl, sufentanil or alfentanil (ALF) suppressed the response to noxious and surgical stimuli, providing profound analgesia.[5]

Although there are reports using a constant rate infusion (CRI) of propofol and short-acting opioids in cats,[1,5,6] there are no published clinical studies comparing infusion rates of propofol and remifentanil (REMI) or ALF in cats undergoing surgery. The aim of this study was to compare the cardiovascular and anesthetic effects of continuous variable-infusion rates of REMI or ALF in propofol-anesthetized cats undergoing ovariohysterectomy. Dosages of REMI or ALF necessary to attenuate autonomic responses during surgery were also evaluated.

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Materials and methods

The study protocol was approved by the Animal Research Ethics Committee of the School of Veterinary Medicine and Animal Science, Sao Paulo State University, Brazil (protocol number 09/2009).

Animals

Sixteen client-owned domestic mixed-breed cats ranging in weight from 2.4 to 3.3 kg [mean ± standard deviation (SD), 2.87 ± 0.31 kg] were included in a randomized, prospective, clinical trial. Randomization was done via coin toss but when eight animals had been assigned to one group the remainder was placed in the second group. Cats underwent routine ovariohysterectomy with the owner's written consent. They were indoor cats that were considered to be healthy based on medical history and physical examination. Food, but not water, was withheld 12 h before the surgery. According to the owners, cats were young adults but their exact age was unknown.

Anesthesia, surgery and treatments

Cats were premedicated with 0.1 mg/kg of acepromazine (Acepran; Univet) administered by the intramuscular (IM) route. Approximately 20 min after premedication, a cephalic vein was aseptically catheterized, and anesthesia was induced with 5 mg/kg of propofol (Diprivan; AstraZeneca) by the IV route. Propofol was given over approximately 15 s and until a moderate depth of anesthesia (eyeball rotation, absent palpebral reflex and decreased jaw tone) was achieved and intubation with an appropriately sized, cuffed endotracheal tube could be performed. Prior to intubation, the larynx was desensitized with 0.1 ml of lidocaine (Xylestesin 2%; Cristalia). The tube was connected to a Bain-circuit system and 100% oxygen was provided. The fresh gas flow was set at 300 ml/kg/min. After induction of anesthesia, cats were then positioned in dorsal recumbency on a thermal blanket for instrumentation and surgery. Anesthesia was managed by a single observer (STP) and maintained with a CRI of propofol (0.3 mg/kg/min). Five minutes after induction of anesthesia, a bolus injection followed by an infusion of REMI (Ultiva; Glaxo Wellcome) (2.5 µg/kg; 0.2 µg/kg/min) or ALF (Alfast; Cristalia) (10 µg/kg; 0.8 µg/kg/min) was administered to the REMI or ALF group, respectively.

A lactated Ringer's solution was administered at 10 ml/kg/h throughout surgery. In case of hypotension, a fluid bolus of 15 ml/kg was administered over 15 min. All surgical procedures were performed by one experienced surgeon. Using a scalpel blade, a ventral midline incision was performed over the skin, subcutaneous tissue and the linea alba. A standard three-clamp technique was used. The abdominal wall and subcutaneous tissues were closed separately using a simple continuous pattern of absorbable sutures and the skin was closed in a simple interrupted pattern.

Monitoring and time points

Rectal temperature (RT) was monitored with a digital thermometer. Airway gas samples were continuously obtained from the proximal end of the endotracheal tube and analyzed with an infrared gas analyzer to monitor respiratory rate (RR) and end-tidal carbon dioxide concentrations ($ETCO_2$). Cats were allowed to breathe spontaneously but assisted ventilation was manually provided to maintain eucapnia ($ETCO_2$ values from 32 to 37 mmHg).

Heart rate (HR) and systolic arterial pressure (SAP) were monitored using Doppler pulse detection with the cuff placed around the antebrachium; cuff width was approximately 40% of the circumference of the limb. Adhesive electrodes were placed to obtain a continuous lead II ECG. Pulse oximetry (SpO_2) was estimated with a pulse oximeter with an infrared sensor attached to the cat's tongue.

Data were collected 15 min after the beginning of opioid infusions and immediately before skin incision (T0), and then at specific time points during surgery: at the end of skin incision (T1), immediately after celiotomy (T2), during traction and ligation (just before excision) of the left (T3) and right ovary (T4), at the time that the uterus was clamped for performing the hysterectomy (T5), at the midpoint of closure of the abdominal wall (T6), and at the midpoint of skin closure (T7).[5]

Adjustment of infusion settings

Based on cardiovascular responses to surgical stimulation, the opioid infusions were increased or decreased. If SAP and/or HR increased by 20% from previously recorded values in response to surgical stimulation (considering values recorded immediately before one of the aforementioned surgical events), the surgical stimulus was immediately stopped and the infusion rate of REMI or ALF was increased by 10% from the previous value. Then, a period of at least 3 min was allowed before continuing surgery. The 10% increase in the opioid infusion was performed until the increase in SAP and/or HR was no longer observed and, thereafter, the infusion was maintained at that rate. Similarly, if SAP and/or HR decreased by 20% from previously recorded values, the opioid infusion was decreased by 10% and the same interval was allowed before continuing surgery. Opioid infusions were decreased to the initial rate for at least 3 min prior to T6 and increased again, if necessary, following the same described protocol until the end of the procedure. This was undertaken because previous studies showed that maximal nociceptive stimulation occurs at T3 and T4.[5] All infusions were discontinued at the end of the surgery. Surgery time (time elapsed from the first incision until placement of the last suture), anesthesia time (time elapsed from injection of propofol to termination of propofol CRI), and extubation time (time elapsed from termination of propofol CRI until extubation) were recorded for each cat. Time to first head lift, time to attain sternal recumbency, and time to standing (defined as ability to ambulate at least 5 s without assistance) were recorded for each cat. Extubation was performed once the cat's palpebral reflexes were evident and prior to swallowing. Recovery time points were recorded as time elapsed from the end of the infusions to observation of the specified event. After extubation, 0.2 mg/kg of meloxicam (Maxicam; Ourofino Saúde Animal) was administered by the subcutaneous route.

Statistical analysis

Data were analyzed using commercial software (Graphpad Prism software, version 4.00, Graphpad Software, San Diego, California, USA). All data were considered normally distributed and passed normality tests using the Shapiro−Wilk test, with the exception of extubation time. Data within each treatment group were analyzed for changes with time by use of one-way analysis of variance (ANOVA) for repeated measures followed by Dunnett's test, if appropriate. Variables were compared between groups using Student *t*-test or Mann−Whitney test (extubation time), if appropriate, and all differences were considered to be significant at $P < 0.05$.

Results

All the results are expressed as mean ± SD. None of the cats required additional propofol during the study period. There were no significant differences ($P > 0.05$) between groups for body weight, anesthetic duration and surgery time (Table 1). Extubation time was shorter in REMI than in ALF group ($P < 0.05$) (Table 1). This variable was expressed as mean ± standard deviation as both tests used to analyze data (Students *t*-test or Mann−Whitney) detected a significant difference between groups. Time to first head lift and time to attain sternal recumbency were not significantly different ($P > 0.05$) for REMI and ALF groups (Table 1).

In both groups, RT, RR, $ETCO_2$ and SpO_2 values were not significantly different when compared to baseline ($P > 0.05$), with the exception that RT was lower at T7 when compared to baseline ($P < 0.05$). In the ALF group, but not in the REMI group, HR was higher at T4, T5 and T6 when compared to baseline ($P < 0.05$). At T3, SAP was higher in the ALF group and at T4, T5, T6 and T7 in both groups when compared to baseline ($P < 0.05$). From T3 to T7, mean infusion rate of ALF or REMI was significantly higher when compared to baseline ($P < 0.05$). When data were compared between groups, there were no significant differences for RR, $ETCO_2$, HR and SpO_2 ($P > 0.05$). From T2 until T4, SAP was lower in the ALF when compared with the REMI group ($P < 0.05$). Overall, the infusion rates of REMI and ALF were 0.24 ± 0.05 μg/kg/min and 0.97 ± 0.22 μg/kg/min, respectively. Values are presented as mean ± SD in Table 2.

Discussion

This study showed that both combinations of propofol and REMI or ALF provided satisfactory means of TIVA in 16 cats undergoing ovariohysterectomy. However, it should be recognized that these are small numbers of animals and only with use in larger numbers of cats can one truly state that these protocols are safe. Recovery from anesthesia was uneventful in both groups. These findings are in agreement with a previous study in human patients undergoing percutaneous nephrolithotripsy.[3] To the authors' knowledge, there were no published studies comparing REMI or ALF in propofol-anesthetized cats in the clinical setting. In addition, these doses will be useful in clinical practice as there are only a few reports regarding the effects of ultra-short-acting opioids in the cat. In the aforementioned study by Cicek et al,[3] opioid infusions were fixed and administered as a CRI and propofol requirements were adjusted as needed, whereas in the current study, the authors evaluated a fixed dose of propofol while REMI or ALF were titrated to prevent autonomic responses during surgery. This particular study design was chosen based on the fact that propofol may cause moderate to severe cardiovascular depression when used alone or at high dosage regimens during TIVA.[7]

Both REMI and ALF are synthetic opioid drugs that bind to μ (MOP) opioid receptors with different pharmacokinetic profile.[8−10] In cats, it has been suggested that REMI is degraded by non-specific plasma and

Table 1. Body weight, surgery time, anesthetic time and specific recovery times (mean ± SD) in propofol-anesthetized cats ($n = 8$/group) undergoing ovariohysterectomy receiving a continuous infusion of REMI or ALF. Time to extubation is shown as median (range).

Group	Body weight (kg)	Surgery time (min)	Anesthetic time (min)	Time to extubation (min)	Time to head lift (min)	Time to sternal (min)	Time to standing (min)
REMI	2.8 ± 0.3	50.9 ± 13	65.4 ± 15	9.5 (6−10)*	30 ± 12.8	42.5 ± 12.4	62.6 ± 19.5
ALF	2.9 ± 0.3	44.6 ± 12	57.6 ± 13	12 (8−27)	31 ± 17	47.5 ± 30.4	51.8 ± 11.1

*Time to extubation was significantly shorter in the REMI than in the ALF group ($P < 0.05$).

Table 2. Variables (mean ± SD) recorded in propofol-anesthetized cats ($n = 8$/group) undergoing ovariohysterectomy receiving a continuous infusion of REMI or ALF.

Variables	Group	Time points							
		T0	T1	T2	T3	T4	T5	T6	T7
HR (beats/min)	REMI	129 ± 27	130 ± 29	135 ± 29	152 ± 33	160 ± 31	160 ± 35	162 ± 34	163 ± 35
	ALF	112 ± 20	111 ± 20	119 ± 25	135 ± 28	149 ± 27*	154 ± 28*	150 ± 35*	144 ± 36
SAP (mm Hg)	REMI	79.7 ± 16	83 ± 19	89.7 ± 20†	103.2 ± 22†	111 ± 20*,†	113.2 ± 19*	108.5 ± 19*	106.2 ± 27*
	ALF	66.2 ± 10	70.7 ± 12	71.2 ± 12	81 ± 18*	89 ± 18*	93.2 ± 14*	91.2 ± 16*	88.2 ± 18*
RR (breaths/min)	REMI	16 ± 7	14 ± 5	14 ± 5	15 ± 8	14 ± 8	14 ± 6	14 ± 6	12 ± 6
	ALF	14 ± 5	12 ± 4	12 ± 4	11 ± 4	12 ± 6	12 ± 6	13 ± 6	12 ± 5
SpO_2	REMI	98.1 ± 1	98.4 ± 1	98.2 ± 1	98.1 ± 1	98.1 ± 1	98.1 ± 1	98.5 ± 1	98.75 ± 1
	ALF	98.7 ± 1	98.6 ± 1	98.2 ± 1	98 ± 1	98.6 ± 1	98 ± 1	98.4 ± 1	98.2 ± 1
$ETCO_2$	REMI	41.5 ± 3	41.7 ± 2	40.7 ± 2	40.6 ± 2	39 ± 3	40.1 ± 3	41 ± 4	39.1 ± 3
	ALF	40.5 ± 4	39.2 ± 3	39.9 ± 2	39.2 ± 3	38.2 ± 3	37.6 ± 3	39.4 ± 3	39 ± 3
RT (°C)	REMI	37.1 ± 0.7	37 ± 0.6	36.7 ± 0.6	36.4 ± 0.6	36.2 ± 0.6	36.1 ± 0.5	36 ± 0.5	35.9 ± 0.5*
	ALF	37.5 ± 0.5	37.3 ± 0.5	37.2 ± 0.5	36.7 ± 0.4	36.4 ± 0.5	36.2 ± 0.5	36 ± 0.4	35.9 ± 0.4*
CRI (μg/kg/min)	REMI	0.2 ± 0	0.2 ± 0	0.2 ± 0	0.27 ± 0.06*	0.28 ± 0.05*	0.28 ± 0.05*	0.28 ± 0.06*	0.28 ± 0.06*
	ALF	0.8 ± 0	0.8 ± 0	0.81 ± 0.03	0.98 ± 0.23*	1.09 ± 0.23*	1.16 ± 0.2*	1.13 ± 0.21*	1.06 ± 0.26*

*Significantly different from baseline values within the group ($P < 0.05$).
†Significantly higher in the REMI than in the ALF group ($P < 0.05$).

tissue esterases.[8,9] Therefore, REMI was characterized by moderate volume of distribution and high clearance which resulted in a short terminal half-life and onset of action.[8,9] This pharmacokinetic and pharmacodynamic profile is of great importance in cats as less prolonged effects are expected clinically even after long periods of infusion. Hypothetically, cats with liver or renal insufficiency should not experience prolonged anesthetic recovery as has been demonstrated in humans.[11,12] REMI is commercially available in a lyophilized form to be diluted in normal saline or 5% glucose solution. The solution expires 24 h after its preparation and this may be a disadvantage when compared with other ultra-short opioids.

Recent studies in cats have reported that REMI reaches peak plasma concentration a few minutes after starting infusion.[8,9] However, this study was conducted before such reports and the authors had opted to administer a loading dose before beginning the infusion based on the fact that peak effect might take several minutes to occur. The doses of propofol and REMI were based on a prospective clinical study where a combination of propofol (0.3 mg/kg/min) and REMI (0.2–0.23 μg/kg/min) provided satisfactory depth of anesthesia in cats undergoing ovariohysterectomy.[6]

ALF has also a rapid onset of action but unlike REMI the drug depends on hepatic metabolism and is excreted by the kidneys.[10] Immediately after a 50 μg/kg IV bolus, ALF caused excitement in conscious cats and the duration of analgesia was observed for approximately 20 min.[10] The elimination half-life and volume of distribution are 112 min and 224 ml/kg, respectively, in the cat.[10] In propofol-anesthetized cats, a CRI of ALF (0.5 μg/kg/min) suppressed movement response to toe pinching.[5] Based on the study by Mendes et al[5] and the authors' clinical experience, an initial infusion rate of 0.8 μg/kg/min of ALF was chosen.

In between time points, when the opioid infusion had to be increased due to autonomic responses to surgery, at least 3 min were allowed before continuing the procedure. The authors realize that increases in infusion rate may have been more effective in the REMI group compared with the ALF group due to differences in the pharmacokinetics of these opioids. However, anesthetic time would have been different between groups if the authors had based their surgical delay on pharmacokinetic data. The ALF group would have been anesthetized for longer due to its longer half-life when compared with REMI. This would have significantly affected the effects of propofol and/or the opioid on recovery times.

In the ALF but not in the REMI group, HR was significantly higher at time points (T4, T5 and T6) during surgery when compared to baseline. In the ALF group, HR baseline values (mean ± SD, 112 ± 20 bpm) were close to what the authors had considered to be bradycardia (<100 bpm). The decreases in HR may have been secondary to the anesthetic effects of propofol leading to a deep plane of anesthesia and/or due to vagal stimulation caused by ALF in the absence of surgical stimulus.[5,6] In the clinical setting, bradycardia could have been treated with the administration of an anti-cholinergic drug.[13] On the other hand, surgical stimulus may have induced higher HR values at T4, T5 and T6 due to autonomic nervous system activation.

Opioid infusion requirements and SAP were also significantly higher at T3 in the ALF group and at T4, T5, T6 and T7 in both groups when compared to baseline. These results were most likely to be associated with intense surgical stimulation and/or with an increase in sympathetic nervous system activity. Although opioids generally lead to a decrease in HR and SAP, cats may show signs of cardiovascular stimulation secondary to sympathetic activation due to high doses of ultra-short-acting opioid drugs.[14,15] In cats anesthetized with isoflurane, IV administration of REMI[14] or ALF[15] resulted in elevated SAP and HR. This was consistent with an increase in plasma concentrations of catecholamines.[15] The SAP was significantly lower in the ALF group compared with REMI group from T2 to T4. At those time points, mild hypotension was observed in both treatments. This could be attributed to minimal surgical manipulation but peripheral vasodilation secondary to the administration of acepromazine may have played a role on this phenomenon. Propofol may also have contributed to hypotension, as this drug reduces peripheral vascular resistance and causes myocardial depression.[7] Lastly, indirect blood pressure monitoring was performed by means of Doppler ultrasound. This device has been shown to provide consistent prediction of mean and not SAP in cats[16] where the latter was underestimated by about 15 mmHg when compared with direct blood pressure measurements.[17] Therefore, in the present study, blood pressure values may have been an underestimation of SAP and cats may not have been truly hypotensive.

The administration of opioids and propofol is associated with respiratory depression and hypercapnia in a dose-dependent manner.[4,18] For this reason, cats were allowed to breathe spontaneously but intermittent assisted ventilation was provided in order to maintain eucapnia ($ETCO_2$ values from 32 to 37 mmHg). This study was not designed to compare the respiratory depressant effects of ALF or REMI.

RT was significantly decreased at T8 when compared to baseline in both treated groups. Hypothermia could have been affected by the administration of acepromazine which induces peripheral vasodilation by blocking α_1 receptors but also interferes with the thermoregulatory center.[19] Clinical experience suggests that normothermic animals recover faster from anesthesia when compared with hypothermic individuals.

Anesthetic recovery may be prolonged in cats receiving a CRI of propofol for more than 30 min.[18] In the present study, recovery time was probably reasonable because cats were given a propofol-opioid infusion for approximately an hour. Prolonged propofol infusions may cause significantly delayed anesthetic recoveries in cats.[18] Extubation time was significantly shorter in the REMI group when compared with ALF-treated cats, even though time to first head lift and time to attain sternal recumbency were not significantly different between groups. Similar findings have been reported in a clinical trial in humans.[3] REMI has rapid elimination and clearance,[8,9] and usually does not prolong anesthetic recovery.

In summary, the administration of REMI or ALF provided effective and satisfactory anesthesia in propofol-anesthetized cats undergoing ovariohysterectomy. Side effects were not observed in this study. Nevertheless, assisted ventilation was provided and marked respiratory depression could have occurred otherwise. Cats that were treated with REMI presented earlier extubation time when compared with cats in the ALF group. In order to suppress autonomic nervous stimulation during surgery, infusion rates of 0.24 ± 0.05 μg/kg/min and 0.97 ± 0.22 μg/kg/min for REMI and ALF, respectively, are recommended.

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