Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2013, **40**, 599–609 doi:10.1111/vaa.12079

RESEARCH PAPER

Evaluation of the isoflurane-sparing effects of fentanyl, lidocaine, ketamine, dexmedetomidine, or the combination lidocaine-ketamine-dexmedetomidine during ovariohysterectomy in dogs

Eduardo Gutierrez-Blanco*,†, José M Victoria-Mora‡, Jose A Ibancovichi-Camarillo†, Carlos H Sauri-Arceo*, Manuel E Bolio-González*, Carlos M Acevedo-Arcique†, Gabriela Marin-Cano* & Paulo VM Steagall§

*Department of Animal Health and Preventive Medicine, Faculty of Veterinary Medicine, Yucatan Autonomous University, Merida, Mexico

†Department of Veterinary Anesthesiology, Faculty of Veterinary Medicine, Mexico State Autonomous University, Toluca, Mexico

‡Department of Veterinary Orthopedics and Traumatology, Faculty of Veterinary Medicine, Mexico State Autonomous University, Toluca, Mexico

§Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, Saint-Hyacinthe, QC, Canada

Correspondence: Paulo VM Steagall, Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Montreal, 3200, rue Sicotte, Saint-Hyacinthe, QC, J2S 2M2, Canada. E-mail: psteagall@gmail.com

Abstract

Objective To evaluate the isoflurane-sparing effects of an intravenous (IV) constant rate infusion (CRI) of fentanyl, lidocaine, ketamine, dexmedetomidine, or lidocaine-ketamine-dexmedetomidine (LKD) in dogs undergoing ovariohysterectomy.

Study design Randomized, prospective, blinded, clinical study.

Animals Fifty four dogs.

Methods Anesthesia was induced with propofol and maintained with isoflurane with one of the following IV treatments: butorphanol/saline (butorphanol 0.4 mg kg^{-1}, saline 0.9% CRI, CONTROL/BUT); fentanyl (5 μg kg^{-1}, 10 μg kg^{-1} $hour^{-1}$, FENT); ketamine (1 mg kg^{-1}, 40 μg kg^{-1} $minute^{-1}$, KET), lidocaine (2 mg kg^{-1}, 100 μg kg^{-1} $minute^{-1}$, LIDO); dexmedetomidine (1 μg kg^{-1}, 3 μg kg^{-1} $hour^{-1}$, DEX); or a LKD combination. Positive pressure ventilation maintained eucapnia. An anesthetist unaware of treatment and end-tidal isoflurane concentration (FE′Iso) adjusted vaporizer settings to maintain surgical anesthetic depth. Cardiopulmonary variables and FE′Iso concentrations were monitored. Data were analyzed using ANOVA ($p < 0.05$).

Results At most time points, heart rate (HR) was lower in FENT than in other groups, except for DEX and LKD. Mean arterial blood pressure (MAP) was lower in FENT and CONTROL/BUT than in DEX. Overall mean ± SD FE′Iso and % reduced isoflurane requirements were 1.01 ± 0.31/41.6% (range, 0.75 ± 0.31/56.6% to 1.12 ± 0.80/35.3%, FENT), 1.37 ± 0.19/20.8% (1.23 ± 0.14/28.9% to 1.51 ± 0.22/12.7%, KET), 1.34 ± 0.19/22.5% (1.24 ± 0.19/28.3% to 1.44 ± 0.21/16.8%, LIDO), 1.30 ± 0.28/24.8% (1.16 ± 0.18/32.9% to 1.43 ± 0.32/17.3%, DEX), 0.95 ± 0.19/54.9% (0.7 ± 0.16/59.5% to 1.12 ± 0.16/35.3%, LKD) and 1.73 ± 0.18/0.0% (1.64 ± 0.21 to 1.82 ± 0.14, CONTROL/BUT) during surgery. FENT and LKD significantly reduced FE′Iso.

Conclusions and clinical relevance At the doses administered, FENT and LKD had greater isoflurane-sparing effect than LIDO, KET or CONTROL/BUT, but not at all times. Low HR during FENT may limit improvement in MAP expected with reduced F_E'Iso.

Keywords analgesia, anesthesia, balanced anesthesia, dog, isoflurane.

Introduction

Inhalation anesthetics have been widely used for anesthetic maintenance in veterinary medicine. Main advantages include rapid control of the anesthetic depth by adjustments of the vaporizer dial and fresh oxygen flow, and favorable pharmacokinetic profile, allowing relatively rapid induction and recovery from anesthesia because anesthetic gas uptake and elimination occurs mainly via the lungs (Steffey & Howland 1977). However, one of the main concerns is the progressive cardiopulmonary depression observed with high doses of inhalation agents such as isoflurane (ISO). High risk patients or animals with systemic disease may develop severe cardiovascular depression if anesthesia is maintained with an inhalation anesthetic alone. Consequently, anesthetic agents such as fentanyl, lidocaine, ketamine and/or dexmedetomidine have been used in an attempt to reduce inhalation agent requirements resulting in less cardiovascular depression (Wagner et al. 2002; Muir et al. 2003; Valverde et al. 2004; Pascoe et al. 2006; Sano et al. 2006; Solano et al. 2006; Steagall et al. 2006; Lin et al. 2008; Uilenreef et al. 2008; Matsubara et al. 2009; Ueyama et al. 2009; Ortega & Cruz 2011; Columbano et al. 2012). Combinations of drugs with different pharmacologic mechanisms may provide greater analgesia than each drug given alone, with further inhalant-sparing effect (Muir et al. 2003; Doherty et al. 2007; Wilson et al. 2008; Aguado et al. 2011).

The aim of this study was to evaluate the ISO-sparing effects of a continuous rate infusion (CRI) of fentanyl (FENT), lidocaine (LIDO), ketamine (KET), dexmedetomidine (DEX) on separate occasions, or the combination lidocaine-ketamine-dexmedetomidine (LKD) in dogs undergoing ovariohysterectomy. The authors hypothesized that all drug treatments would reduce the ISO requirements in comparison to a control group administered a single dose of butorphanol (CONTROL/BUT). This ISO-sparing effect would lead to less hypotension during anesthesia and surgery in the treated groups.

Materials and methods

The study protocol was approved by the Animal Research Ethics Committee of the Faculty of Veterinary Medicine, Mexico State Autonomous University, Mexico (protocol number FE44/2009- 103.5/09/4195).

Animals

Fifty four client-owned mixed-breed intact non pregnant female dogs (1–6 years old) were enrolled in a randomized, prospective, blinded clinical study after the owner's written consent was obtained. The dogs were considered to be healthy based on medical history, physical examination, complete blood count (CBC) and serum biochemical analyses. Dogs with abnormal laboratory data or any clinical signs of systemic disease were not included in the study.

Anesthetic procedure and treatments

Food but not water was withheld for 10 hours before anesthesia. Approximately 5 minutes before induction of anesthesia, an arterial blood sample was collected percutaneously from the femoral artery in heparinized syringes (Pro-vent Plus 1 mL; Smiths Medical, MN, USA), and immediately analyzed for arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial pH (pHa), bicarbonate (HCO_3^-), lactate and glucose concentrations (IL GEM Premier 3000, Instrumentation Laboratory, MA, USA). Blood-gas measurements were corrected to body temperature.

A 20-gauge catheter was aseptically placed into a cephalic vein and connected to a resealable male luer injection port (BD-luer loK; Becton Dickinson and Company, NJ, USA). Saline 0.9% (Solucion DX-CS; Pisa Farmaceutica, Mexico) was administered at 3 mL kg^{-1} $hour^{-1}$ throughout anesthesia by the use of a syringe infusion device (Graseby 3400; Graseby Medical, UK). Anesthesia was induced by administration of propofol (6 mg kg^{-1}; Diprivan; Zeneca Pharma, Mexico) IV over 1 minute. The dogs were intubated with appropriately sized cuffed endotracheal tubes and connected to a rebreathing system (Multiplus MEVD; Royal Medical Co. Ltd., South Korea). ISO (Isoflurane USP, Piramal Health Care, India) in 100% oxygen was adminis-

tered for maintenance of anesthesia, with an initial oxygen flow rate of approximately 100 mL kg^{-1} $minute^{-1}$ that was reduced to approximately 50 mL kg^{-1} $minute^{-1}$ after 15 minutes. Intermittent positive pressure ventilation (IPPV) was started at the beginning of anesthesia (Vent V; Royal Medical Co. Ltd) and adjusted to maintain eucapnia (end-tidal carbon dioxide tension ($P_E'CO_2$) 33–45 mmHg, 4.4–5.9 kPa). Dogs were then placed in lateral recumbency and a 22-gauge catheter (Introcan; B-Braun, Brazil) was introduced into a dorsal pedal artery for blood pressure monitoring and sampling of arterial blood. A thermal warming blanket (HoMedics HP300-A; HoMedics, China) was used to maintain rectal temperature at 37–38ºC. All surgeries were performed through a ventral midline incision by the same surgeons (FDE/CSA).

Five minutes after induction of anesthesia the dogs were randomly assigned to one of the following treatments:

- Group FENT: A loading dose (5 μg kg^{-1}) of fentanyl (Fentanest; Janssen, Mexico) followed by a CRI of 10 μg kg^{-1} $hour^{-1}$;
- Group KET: A loading dose (1 mg kg^{-1}) of ketamine (Inoketan; Virbac, Mexico) followed by a CRI of 40 μg kg^{-1} $minute^{-1}$;
- Group LIDO: A loading dose (2 mg kg^{-1}) of lidocaine (Pisacaina 2%; Pisa Farmaceutica, Mexico) followed by a CRI of 100 μg kg^{-1} $minute^{-1}$;
- Group DEX: A loading dose (1 μg kg^{-1}) of dexmedetomidine (Dexdormitor; Pfizer Animal Health, Mexico) followed by a CRI of 3 μg kg^{-1} $hour^{-1}$;
- Group LKD: A loading dose (2 mg kg^{-1}) of lidocaine followed by a CRI of 100 μg kg^{-1} $minute^{-1}$, a loading dose (1 mg kg^{-1}) of ketamine followed by a CRI of 40 μg kg^{-1} $minute^{-1}$ and a loading dose (1 μg kg^{-1}) of dexmedetomidine followed by a CRI of 3 μg kg^{-1} $hour^{-1}$;
- Group CONTROL/BUT: A loading dose (0.4 mg kg^{-1}) of IV butorphanol (Torbugesic; Fort Dodge, IA, USA) followed by a CRI of saline 0.9%.

Loading doses were diluted to a final volume of 0.2 mL kg^{-1} with sterile water and administered IV over 2 minutes. In all groups, drugs for CRI were diluted to 60 mL with saline 0.9% and delivered at 2 ml kg^{-1} $hour^{-1}$. All CRIs were started immediately after the loading dose and infused (Colleague 3; Baxter, IN, USA) throughout anesthesia. Surgery commenced 45 minutes after the beginning of CRIs and instrumentation. As part of a different study, at the end of surgery, treatments were not discontinued but instead, doses were decreased and administered for another 4 hours as follows:

- Group FENT: a CRI of 2.5 μg kg^{-1} $hour^{-1}$;
- Group KET: a CRI of 10 μg kg^{-1} $minute^{-1}$;
- Group LIDO: a CRI of 25 μg kg^{-1} $minute^{-1}$;
- Group DEX: a CRI of 1 μg kg^{-1} $hour^{-1}$;
- Group LKD: a CRI of 25 μg kg^{-1} $minute^{-1}$ (LIDO), a CRI of 10 μg kg^{-1} $minute^{-1}$ (KET) and a CRI of 1 μg kg^{-1} $hour^{-1}$ (DEX) in combination;
- Group CONTROL/BUT: a CRI of saline 0.9% at 2 ml kg^{-1} $hour^{-1}$.

Postoperative pain scores were evaluated using four different pain scoring systems and rescue analgesia was provided with IM and subcutaneous administration of morphine (0.5 mg kg^{-1}; Graten; Pisa Farmaceutica, Mexico) and carprofen (4 mg kg^{-1}; Rimadyl; Pfizer Animal Health, NY, USA), respectively. The latter data will be reported elsewhere.

Monitoring, time points and adjustment of vaporizer settings

Inspired ISO (F_IIso) and end-tidal ISO (F_EIso) concentrations, $P_E'CO_2$ and respiratory rate (f_R) were continuously monitored by sampling from the proximal end of the endotracheal tube (V9400 Capnograph Agent monitor; Surgivet, MA, USA). The gas analyzer was calibrated before starting each experiment with a standard gas mixture provided by the manufacturer (Agent Calibration kit, Surgivet).

Heart rate (HR) and rhythm were obtained from a continuous lead II ECG recording. Systolic, mean and diastolic arterial blood pressures (SAP, MAP and DAP, respectively) were continuously monitored (Advisor; Surgivet) from the dorsal pedal artery via saline-filled tubing connected to a pressure transducer (BD DTX Plus; Becton Dickinson and Company). The zero reference point for the pressure transducer was the level of the thoracic inlet while in dorsal recumbency. Hemoglobin oxygen saturation (SpO_2) was monitored with a pulse oximeter (Advisor; Surgivet) with an infrared sensor attached to the dog's tongue. Rectal temperature (RT) was recorded with a digital thermometer. Arterial blood samples were collected for blood-gas analysis at 10, 20, and 30 minutes during surgery and 10 minutes after extubation (POST).

Data were recorded immediately at the beginning of the skin incision (T0, baseline), and then immediately after celiotomy (T1), during traction and ligation (just before excision) of the left (T2) and

right ovary (T3), at the time that the uterus was clamped for performing the hysterectomy (T4), at the midpoint of closure of the abdominal wall (T5), at the midpoint of subcutaneous closure (T6), and at the midpoint of skin closure (T7).

Surgical depth of anesthesia was assessed using the absence of palpebral reflex, lack of jaw tone, and MAP between 60 and 90 mmHg. Higher MAP was accepted if palpebral reflex and jaw tone were absent and no response to surgical stimulation was observed. Decreases in jaw tone were assessed by attempting to open the jaws wide and estimating the amount of passive resistance. Palpebral reflexes were tested by gently tapping the medial canthus of the eye. Based on clinical signs and autonomic responses to surgical stimulation, the vaporizer was adjusted by an anesthetist (EGB) who was blinded to the treatments. If MAP or HR increased by 20% from previously recorded values in response to surgical stimulation at the specified time points, surgery was stopped and isoflurane administration was increased. Surgery continued when MAP or HR values decreased below the initial 20% increment. Conversely, if MAP or HR values decreased by 20%, isoflurane administration was decreased. When MAP decreased to 60 mmHg, 0.9% saline, 5 mL kg^{-1}, was infused over 15 minutes.

Surgery time (time from the first incision until placement of the last suture), anesthesia time (time from injection of propofol to turning off the vaporizer), and time to extubation (time elapsed from turning off the vaporizer dial until extubation) were recorded for each dog. Dogs were disconnected from the rebreathing circuit at extubation. Time to first head lift, time to accomplish sternal recumbency (time elapsed from turning off the vaporizer until sternal recumbency), and time to standing (time elapsed from turning off the vaporizer until standing and defined as ability to stay standing at least 10 seconds without assistance) were recorded for each dog. Extubation was performed once the dogs' cough reflex or swallowing was evident.

Statistical analysis

A Shapiro-Wilk test was used to analyze data and normality. Data are reported as mean ± standard deviation (SD) values, except where indicated. To study temporal changes during anesthesia, a one-way ANOVA for repeated measures was performed for each group followed by Dunnett's test when appropriate. For comparisons between groups, one-way ANOVA was performed at each time point followed by post-hoc Tukey test when appropriate (Graphpad Software 5.0, CA, USA). Differences were considered significant at $p < 0.05$.

Results

Surgery was without complications in all cases and all dogs were discharged from the hospital 24 hours later. There were no significant differences among groups for body weight, anesthetic and surgery times (Table 1). Time to extubation was shorter in LIDO, and KET and CONTROL/BUT when compared with FENT, DEX or LKD, and DEX and LKD, respectively ($p < 0.05$) (Table 1). Time to first head lift was longer in LKD when compared with all other groups ($p < 0.05$). Time to sternal recumbency was shorter in LIDO when compared with FENT, and longer in LKD when compared with all groups, with the exception of FENT ($p < 0.05$). Time to standing was significantly shorter in LIDO when compared with FENT and KET, and longer in LKD when compared with all other groups.

Blood-gas and biochemical variables

Baseline measurements were not significantly different among groups for pH, $PaCO_2$, PaO_2, HCO_3^-, glucose and lactate concentrations (Table 2). Some differences were found at different time points but all values were close to baseline values and unlikely to be of clinical relevance with the exception of glucose concentrations (Table 2).

At 10 and 30 minutes, and at 20 minutes and POST, glucose concentrations were higher in DEX when compared with FENT, LIDO, CONTROL/BUT, and FENT and LIDO, respectively. At 30 minutes and POST, glucose was higher in LKD than in LIDO. Compared with baseline, glucose was significantly higher in DEX (10, 20, 30 minutes and POST), KET (30 minutes and POST) and LKD (20, 30 minutes and POST).

Cardiopulmonary variables

HR was significantly higher at T2 in FENT, LIDO and DEX, at T3 and T4 in DEX, and at T2 and T3 in CONTROL/BUT (Table 3). SAP, MAP and DAP were higher at T2, T3 and T4 when compared with baseline in CONTROL/BUT. SAP, MAP and DAP were higher from T2 to T7 when compared with

Table 1 Body weight, surgery time, anesthetic time and specific recovery times (mean ± SD) in isoflurane-anesthetized dogs undergoing ovariohysterectomy receiving a CRI of fentanyl (loading dose of 5 μg kg^{-1} followed by 10 μg kg^{-1} $hour^{-1}$; FENT), ketamine (loading dose of 1 mg kg^{-1} followed by 40 μg kg^{-1} $minute^{-1}$; KET), lidocaine (loading dose of 2 mg kg^{-1} followed by 100 μg kg^{-1} $minute^{-1}$; LIDO), dexmedetomidine (loading dose of 1 μg kg^{-1} followed by 3 μg kg^{-1} $hour^{-1}$; DEX), a combination of lidocaine-ketamine-dexmedetomidine (LKD) or saline 0.9%/butorphanol (loading dose of 0.4 mg kg^{-1} of IV butorphanol followed by a CRI of saline 0.9%; CONTROL/BUT)

Group	Body weight (kg)	Surgery time (minutes)	Anesthetic time (minutes)	Time to extubation (minutes)	Time to first head lift (minutes)	Time to sternal recumbency (minutes)	Time to standing (minutes)
FENT (n = 10)	15.4 ± 5.9	38.7 ± 8.7	85.8 ± 11.5	12.0 ± 4.9ad	16.1 ± 8bcd	23.9 ± 10.1 cd	36.5 ± 10.2b
KET (n = 8)	15.7 ± 4.7	40.9 ± 7.1	87.5 ± 9.4	7.3 ± 2.7bcd	11.4 ± 4.4c	21 ± 8.3bcd	40.3 ± 13.6bd
LIDO (n = 9)	14.4 ± 5.9	39.3 ± 5.2	85.7 ± 10.8	6.3 ± 1.9bc	9 ± 2.1bc	11.3 ± 2.8b	22.1 ± 5.9c
DEX (n = 8)	17 ± 6.4	41.5 ± 7.6	88.6 ± 12.3	14 ± 4.6a	16.1 ± 5.6bcd	21.3 ± 6.3bcd	28.6 ± 9.3bc
LKD (n = 10)	16 ± 4.6	40 ± 8.3	90.1 ± 12.1	16.5 ± 4.9a	29.6 ± 8.4a	37.5 ± 10.2a	59.9 ± 11.8a
CONTROL/BUT (n = 9)	15.2 ± 6.1	38.9 ± 8.9	86.9 ± 9.7	7.3 ± 2.8bcd	9.7 ± 3.3bc	14.4 ± 3.9bc	26 ± 5.4bc

a,b,c,d significantly different among groups ($p < 0.05$).

baseline in all other groups. Two dogs in the DEX group developed a second degree atrioventricular (A-V) block 3−5 minutes after the loading dose.

f_R, SpO_2 and RT were not significantly different from baseline with any treatment (data not shown). f_R, SpO_2 and RT values were not significantly different among groups ($p > 0.05$). $P_E'CO_2$ was higher in KET and CONTROL/BUT at T2 when compared to LKD and LIDO, respectively (Table 3) ($p < 0.05$). Other significant changes for HR, SAP, MAP and DAP are reported in Table 3.

Isoflurane requirement

F_E'Iso concentrations were higher at T2 and T3, in DEX and lower in FENT, KET, LKD at T6 and T7, respectively, when compared with baseline (Table 4). Overall F_E'Iso, mean ± SD, and % reduction in F_E'Iso (ranges) were 1.01 ± 0.31/41.6% (0.75 ± 0.31/56.6% to 1.12 ± 0.80/35.3%, FENT), 1.37 ± 0.19/20.8% (1.23 ± 0.14/28.9% to 1.51 ± 0.22/12.7%, KET), 1.34 ± 0.19/22.5% (1.24 ± 0.19/28.3% to 1.44 ± 0.21/16.8%, LIDO), 1.30 ± 0.28/24.8% (1.16 ± 0.18/32.9% to 1.43 ± 0.32/17.3%, DEX), 0.95 ± 0.19/54.9% (0.7 ± 0.16/59.5% to 1.12 ± 0.16/35.3%, LKD) and 1.73 ± 0.18/0.0% (1.64 ± 0.21 to 1.82 ± 0.14, CONTROL/BUT). F_E'Iso was significantly reduced in FENT and LKD at different time points than other groups. F_E'Iso was significantly higher in CONTROL/BUT than in other groups throughout surgery.

Discussion

The results of this study show that, in comparison with the control group, all treatments were associated with significant decreases in F_E'Iso, and such findings were in accordance with the authors' hypothesis. However, this isoflurane-sparing effect did not always provide significantly higher blood pressures during anesthesia and surgery. The opioid vagal-mediated bradycardia (Steagall et al. 2006) produced by FENT may have partially prevented a greater increase in MAP that would be expected with reduced inhalant anesthetic administration. For any interpretation of data, one must bear in mind that all comparisons in this study were made with a group that had been administered a single dose of butorphanol, a drug that produces reduction in the minimum alveolar concentration of isoflurane (MAC_{ISO}) in dogs (Ko et al. 2000). However, butorphanol is a short-acting opioid analgesic (Camargo et al. 2011) and decreases in isoflurane requirements would be also short-lived since plasma concentrations of the drug would be expected to decline over time.

HR was lower in the FENT group compared with the other groups, with the exception of DEX and LKD, throughout the surgery. Opioids may induce an increase in vagal tone leading to bradycardia (Steagall et al. 2006) and anticholinergic drugs have been used to prevent or treat opioid-induced bradycardia (Ilkiw et al. 1993; Dyson & James-Davies 1999). In this case, an improvement in arterial blood pressure and HR would have been

Table 2 Arterial blood variables (mean ± SD) recorded in isoflurane-anesthetized dogs undergoing ovariohysterectomy receiving either a CRI of fentanyl (FENT), ketamine (KET), lidocaine (LIDO), dexmedetomidine (DEX), lidocaine-ketamine-dexmedetomidine (LKD) or saline 0.9% (CONTROL/BUT). See Table 1 for dosage regimens

Variables	Group	Baseline	10 minutes	20 minutes	30 minutes	Post
pH	FENT	7.33 ± 0.06	7.34 ± 0.04	7.31 ± 0.03	7.31 ± 0.03	7.29 ± 0.04a
	KET	7.38 ± 0.03	7.32 ± 0.05*	7.29 ± 0.06a*	7.33 ± 0.03*	7.33 ± 0.03
	LIDO	7.38 ± 0.02	7.40 ± 0.07	7.38 ± 0.04b	7.37 ± 0.03	7.39 ± 0.04b
	DEX	7.39 ± 0.03	7.36 ± 0.04	7.34 ± 0.03	7.34 ± 0.03	7.37 ± 0.02b
	LKD	7.40 ± 0.03	7.35 ± 0.05	7.33 ± 0.04*	7.32 ± 0.04*	7.38 ± 0.05b
	CONTROL/BUT	7.32 ± 0.05	7.32 ± 0.08	7.30 ± 0.06	7.31 ± 0.08	7.32 ± 0.05
$PaCO_2$ (mmHg and kPa)	FENT	37 ± 4.4	37 ± 2.4	35 ± 3.6	34 ± 4.4	39 ± 4.7abd
		5.0 ± 0.6	4.9 ± 0.3	4.7 ± 0.5	4.6 ± 0.6	5.2 ± 0.6
	KET	38 ± 2.5	36 ± 2.6	38 ± 1.1	35 ± 2.3	37 ± 3.8bc
		5.0 ± 0.3	4.7 ± 0.3	5.0 ± 0.2	4.7 ± 0.3	4.9 ± 0.5
	LIDO	37 ± 4.2	36 ± 4.9	37 ± 1.8	34 ± 1.5	46 ± 5.5a*
		5.0 ± 0.6	4.8 ± 0.6	4.9 ± 0.2	4.6 ± 0.2	6.1 ± 0.7
	DEX	35 ± 2.6	35 ± 3.2	33 ± 1.9b	34 ± 2.4	30 ± 0.9c*
		4.6 ± 0.3	4.7 ± 0.4	4.4 ± 0.3	4.5 ± 0.3	3.9 ± 0.1
	LKD	36 ± 4.1	38 ± 5.9	37 ± 3.2	37 ± 2.1	36 ± 4.5bc
		4.8 ± 0.6	5.1 ± 0.8	5.0 ± 0.4	4.9 ± 0.3	4.7 ± 0.6
	CONTROL/BUT	37 ± 3.1	39 ± 4.9	39 ± 1.8a	38 ± 3.5	37 ± 4.1bc
		5.0 ± 0.4	5.1 ± 0.7	5.3 ± 0.2	5.0 ± 0.5	4.9 ± 0.5
PaO_2 (mmHg and kPa)	FENT	98 ± 6.5	496 ± 73	518 ± 69	516 ± 78	105 ± 12b
		13.1 ± 0.9	66.2 ± 9.7	69.1 ± 9.2	68.8 ± 10.4	14.0 ± 1.6
	KET	97 ± 2	569 ± 58	567 ± 72	587 ± 67	99 ± 4
		12.9 ± 0.3	75.8 ± 7.8	75.6 ± 9.6	78.2 ± 9.0	13.2 ± 0.6
	LIDO	98 ± 4	558 ± 43	593 ± 35	547 ± 56	89 ± 2a*
		13.1 ± 0.5	74.3 ± 5.7	79.1 ± 4.7	73.0 ± 7.5	11.9 ± 0.2
	DEX	96 ± 9	557 ± 65	532 ± 66	561 ± 61	111 ± 12b*
		12.7 ± 1.2	74.3 ± 8.7	70.9 ± 8.8	74.8 ± 8.1	14.9 ± 1.7
	LKD	98 ± 5	532 ± 52	577 ± 27	557 ± 43	99 ± 9
		13.1 ± 0.7	71.0 ± 6.9	76.9 ± 3.7	74.2 ± 5.7	13.2 ± 1.2
	CONTROL/BUT	101 ± 4.7	581 ± 69	559 ± 73	543 ± 68	108 ± 9b
		13.4 ± 0.6	77.4 ± 9.2	74.5 ± 9.8	72.4 ± 9.1	14.4 ± 1.2
HCO_3^- (mmol L^{-1})	FENT	21.1 ± 2.0	19.2 ± 2.5*	18.7 ± 2.0*	18.7 ± 2.0*	19.1 ± 2.1*
	KET	21.7 ± 2.1	19.5 ± 2.3*	18.6 ± 2.2*	19.1 ± 1.6*	19.6 ± 1.3*
	LID	21.0 ± 1.8	21.4 ± 2.4	21.1 ± 2.1	20.5 ± 1.5	22.1 ± 3.2
	DEX	22.0 ± 1.4	19.9 ± 1.7*	19.1 ± 1.3*	19.5 ± 1.0*	19.9 ± 1.1*
	LKD	21.4 ± 1.7	20.3 ± 2.6	20.0 ± 1.4	20.0 ± 1.6	20.4 ± 1.7
	CONTROL/BUT	20.6 ± 2.6	20.8 ± 1.8	19.6 ± 2.2	18.6 ± 2.7*	19.4 ± 1.7
Glucose (mg dL^{-1})	FENT	106 ± 17	91 ± 15b	98 ± 22 cd	113 ± 22bc	119 ± 23bc
	KET	105 ± 14	112 ± 10	122 ± 10abc	132 ± 20abc*	136 ± 29*
	LIDO	97 ± 11	100 ± 9b	103 ± 10bc	94 ± 7c	100 ± 10c
	DEX	93 ± 12	137 ± 18a*	155 ± 34a*	167 ± 22a*	166 ± 25a*
	LKD	93 ± 5	112 ± 15	131 ± 22ab*	141 ± 27ab*	149 ± 38ab*
	CONTROL/BUT	100 ± 6	97 ± 22b	111 ± 5bc	108 ± 16bc	119 ± 16
Lactate (mmol L^{-1})	FENT	1.3 ± 0.4	1.4 ± 0.5	1.7 ± 0.7*	1.9 ± 0.9*	1.9 ± 1.1*
	KET	1.2 ± 0.2	2.0 ± 0.7*	1.9 ± 0.4*	1.9 ± 0.4	1.8 ± 0.4
	LIDO	1.0 ± 0.4	1.5 ± 0.7	1.8 ± 0.7	1.7 ± 0.4	1.2 ± 0.4b
	DEX	1.1 ± 0.3	1.6 ± 0.5*	1.9 ± 0.4*	2.2 ± 0.5*	1.9 ± 0.5*
	LKD	1.2 ± 0.4	1.4 ± 0.5	1.6 ± 0.6*	1.7 ± 0.6*	1.4 ± 0.6b
	CONTROL/BUT	1.5 ± 0.6	1.9 ± 0.8	2.3 ± 1.0	2.3 ± 1.1	2.8 ± 1.2a*

*Significantly different from baseline values ($p < 0.05$). a, b, c, d, e significantly different among groups ($p < 0.05$).

evident in the opioid-treated group as it has been observed in the clinical setting (Steagall et al. 2006). HR was rarely different among FENT, DEX and LKD since a baroreflex physiological bradycardia is commonly observed after the administration of dexmedetomidine due to increases in systemic

Table 3 Variables (mean ± SD) recorded in isoflurane-anesthetized dogs undergoing ovariohysterectomy receiving either a CRI of fentanyl (FENT), ketamine (KET), lidocaine (LIDO), dexmedetomidine (DEX), lidocaine-ketamine-dexmedetomidine (LKD) or saline 0.9%/butorphanol (CONTROL/BUT). See Table 1 for dosage regimens

		Time points							
Variables	Group	T0	T1	T2	T3	T4	T5	T6	T7
HR (beats minute$^{-1)}$	FENT	56 ± 10c	56 ± 10bc	73 ± 24cd*	65 ± 23b	61 ± 21b	55 ± 16c	55 ± 16de	57 ± 16c
	KET	105 ± 20a	107 ± 20a	115 ± 23ae*	108 ± 18ac	109 ± 17ad	100 ± 23ab	102 ± 18ac*	111 ± 15de
	LIDO	106 ± 20a	101 ± 13a	118 ± 18ae*	109 ± 12ac	99 ± 12ac	98 ± 14ab	97 ± 15abc	99 ± 16abd
	DEX	71 ± 14bc	72 ± 17bc	92 ± 21bcde*	90 ± 24bc*	86 ± 19cd*	79 ± 20bc	77 ± 19bd	79 ± 18abc
	LKD	78 ± 17b	76 ± 16b	82 ± 14bc	85 ± 16bc	80 ± 12bc	78 ± 12bc	74 ± 16be	72 ± 14c
	CONTROL/BUT	104 ± 7a	104 ± 18a	129 ± 10a*	129 ± 15a*	115 ± 7a	114 ± 18a	109 ± 21a	104 ± 19ab
SAP (mmHg)	FENT	79 ± 8a	81 ± 8a	117 ± 13*	123 ± 18*	113 ± 11a*	103 ± 14b*	103 ± 17ac*	105 ± 14ac*
	KET	88 ± 6	92 ± 14	124 ± 17*	126 ± 15*	125 ± 11*	112 ± 10*	114 ± 8*	116 ± 12*
	LIDO	102 ± 15b	101 ± 11b	132 ± 10*	125 ± 6*	115 ± 8*	114 ± 12*	113 ± 13*	116 ± 11*
	DEX	100 ± 10b	106 ± 11b	135 ± 8*	134 ± 11*	131 ± 9b*	125 ± 6a*	126 ± 9b*	127 ± 11b*
	LKD	104 ± 11b	106 ± 9b	124 ± 10*	126 ± 9*	121 ± 11*	117 ± 14*	119 ± 15bc*	120 ± 17*
	CONTROL/BUT	86 ± 16	89 ± 21	125 ± 22*	120 ± 21*	115 ± 22*	100 ± 22b	97 ± 20a	97 ± 25a
DAP (mmHg)	FENT	47 ± 7a	51 ± 10a	89 ± 18a*	93 ± 21*	78 ± 10d*	72 ± 13ad*	73 ± 19ad*	73 ± 13ac*
	KET	65 ± 16	67 ± 14	96 ± 8*	95 ± 6*	95 ± 11b*	83 ± 7bcd*	83 ± 7*	89 ± 10*
	LIDO	75 ± 17b	75 ± 13b	102 ± 9*	97 ± 9*	90 ± 13*	86 ± 9cd*	87 ± 11*	85 ± 11*
	DEX	67 ± 13c	78 ± 12c*	110 ± 9b*	107 ± 6b*	102 ± 5bc*	95 ± 6bc*	92 ± 4bc*	94 ± 2b*
	LKD	79 ± 11d	83 ± 9d	101 ± 11*	103 ± 9*	97 ± 11b*	92 ± 12b*	92 ± 13b*	91 ± 11bc*
	CONTROL/BUT	56 ± 17abc	61 ± 22abc	87 ± 21*	82 ± 16a*	74 ± 14a*	63 ± 17a	62 ± 20a	61 ± 18a
MAP (mmHg)	FENT	62 ± 5ad	64 ± 8a	101 ± 14a*	106 ± 19*	95 ± 11b*	87 ± 13ac*	87 ± 18b*	89 ± 14*
	KET	73 ± 15	76 ± 14	107 ± 11*	106 ± 8*	107 ± 10*	94 ± 8*	95 ± 7*	99 ± 10*
	LIDO	83 ± 14b	86 ± 12	113 ± 8*	109 ± 6*	100 ± 12*	96 ± 10*	96 ± 10*	97 ± 10*
	DEX	79 ± 11	89 ± 9b*	119 ± 8b*	116 ± 6*	112 ± 5a*	105 ± 5b*	104 ± 4a*	106 ± 2b*
	LKD	89 ± 11bc	91 ± 8b	109 ± 10*	111 ± 9*	105 ± 10*	102 ± 12bc*	102 ± 13*	102 ± 13*
	CONTROL/BUT	69 ± 18a	70 ± 22	100 ± 20*	97 ± 18*	90 ± 17b*	78 ± 18a	78 ± 21b	77 ± 19a
$P_{E'}CO_2$ (mmHg and kPa)	FENT	34.5 ± 1.4	35.2 ± 2.1	35.9 ± 1.7	35.6 ± 1.9	35.1 ± 1.1	35.4 ± 1.7	36.3 ± 1.7	36.4 ± 1.7
		4.6 ± 0.2	4.7 ± 0.3	4.8 ± 0.2	4.7 ± 0.3	4.7 ± 0.3	4.7 ± 0.1	4.8 ± 0.2	4.9 ± 0.2
	KET	35.8 ± 2.3	36.0 ± 2.0	37.0 ± 2.1ac	36.1 ± 2.5	37.3 ± 1.3	36.6 ± 1.6	36.1 ± 2.8	35.5 ± 2.6
		4.8 ± 0.3	4.8 ± 0.3	4.9 ± 0.3	4.8 ± 0.3	5.0 ± 0.2	4.9 ± 0.2	4.8 ± 0.4	4.7 ± 0.3
	LIDO	35.8 ± 2.0	35.1 ± 2.0	35.3 ± 1.5bc	36.4 ± 1.9	36.0 ± 1.9	36.4 ± 2.1	35.4 ± 2.0	35.6 ± 1.8
		4.8 ± 0.3	4.7 ± 0.3	4.7 ± 0.2	4.9 ± 0.3	4.8 ± 0.3	4.9 ± 0.3	4.7 ± 0.3	4.7 ± 0.2
	DEX	35.5 ± 2.3	34.8 ± 2.3	35.5 ± 1.1	35.8 ± 2.5	36.4 ± 2.1	35.9 ± 1.5	35.8 ± 2.5	36.3 ± 2.2
		4.7 ± 0.3	4.6 ± 0.3	4.7 ± 0.1	4.8 ± 0.3	4.8 ± 0.3	4.8 ± 0.2	4.8 ± 0.3	4.8 ± 0.3
	LKD	35.0 ± 1.9	35.4 ± 2.0	34.5 ± 1.6b	35.6 ± 1.4	36.6 ± 2.2*	36.6 ± 2.2*	37.0 ± 2.3*	36.9 ± 1.9*
		4.7 ± 0.3	4.7 ± 0.3	4.6 ± 0.3	4.7 ± 0.2	4.9 ± 0.2	4.9 ± 0.3	4.9 ± 0.3	4.9 ± 0.2
	CONTROL/BUT	36.6 ± 2.1	36.6 ± 2.5	37.9 ± 1.5a	36.7 ± 1.1	37.1 ± 0.9	37.3 ± 1.6	37.9 ± 1.3	37.3 ± 2.6
		4.9 ± 0.3	4.9 ± 0.3	5.0 ± 0.2	4.9 ± 0.1	5.0 ± 0.1	5.0 ± 0.2	5.0 ± 0.2	5.0 ± 0.3

*Significantly different from baseline values ($p < 0.05$). a, b, c, d, e significantly different among groups ($p < 0.05$).

© 2013 Association of Veterinary Anaesthetists and the American College of Veterinary Anesthesia and Analgesia.

Table 4 F_E'Iso (mean ± SD) recorded in isoflurane-anesthetized dogs undergoing ovariohysterectomy receiving either a CRI of fentanyl (FENT), ketamine (KET), lidocaine (LIDO), dexmedetomidine (DEX), lidocaine-ketamine-dexmedetomidine (LKD) or saline 0.9% - butorphanol (CONTROL/BUT)

	Time points							
Group	**T0**	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**
FENT	1.10 ± 0.24bd	1.12 ± 0.28bd	1.12 ± 0.37b	1.06 ± 0.36bd	1.05 ± 0.33bc	1.01 ± 0.34bc	0.86 ± 0.28be*	0.75 ± 0.31be*
KET	1.43 ± 0.20ac	1.44 ± 0.21ac	1.42 ± 0.23	1.51 ± 0.22ac	1.37 ± 0.15ac	1.32 ± 0.15ac	1.23 ± 0.14cd*	1.24 ± 0.17cd*
LIDO	1.35 ± 0.14cd	1.38 ± 0.17cd	1.44 ± 0.21	1.42 ± 0.25acd	1.32 ± 0.23abc	1.27 ± 0.19cd	1.26 ± 0.16cd	1.24 ± 0.19cd
DEX	1.16 ± 0.26cd	1.16 ± 0.18cd	1.43 ± 0.34*	1.43 ± 0.32ad*	1.38 ± 0.32ac	1.35 ± 0.31ac	1.25 ± 0.27c	1.21 ± 0.26c
LKD	1.01 ± 0.16b	1.00 ± 0.16b	1.12 ± 0.16b	1.02 ± 0.22b	0.98 ± 0.24b	0.91 ± 0.24b	0.83 ± 0.22b*	0.70 ± 0.16b*
CONTROL/BUT	1.74 ± 0.18a	1.73 ± 0.19a	1.80 ± 0.18a	1.82 ± 0.14a	1.74 ± 0.19a	1.69 ± 0.19a	1.64 ± 0.21a	1.65 ± 0.20a

*Significantly different from baseline values (T0) within the group ($p < 0.05$). [a,b,c,d] significantly different among groups ($p < 0.05$).

vascular resistance resulting from an alpha$_2$-mediated vasoconstriction in the peripheral blood vessels (Pascoe et al. 2006). Based on previous studies of the cardiovascular effects of dexmedetomidine (Congdon et al. 2013), it is likely that its administration (DEX and LKD groups) increased systemic vascular resistance that would have countered the isoflurane-induced vasodilation.

Short acting opioids such as FENT, a synthetic μ (OP3) agonist, have been used to improve analgesia during general anesthesia while providing inhalant anesthetic-sparing effects. Fentanyl has been associated with good hemodynamic stability, although bradycardia and mild respiratory depression have been reported in dogs (Sano et al. 2006). In a recent study in dogs, MAC_{ISO} was decreased by 35% after a loading dose of fentanyl (5 μg kg^{-1}) followed by a CRI of 9 μg kg^{-1} hour^{-1} (Ueyama et al. 2009). These findings are consistent with our study, where at similar doses, a 41.6% overall reduction in ISO requirements was observed. In dogs undergoing unilateral mastectomy, decreases in ISO requirements ranged from 54 to 66% after a CRI of 30 μg kg^{-1} hour^{-1} of FENT, a three-fold dosage increase in comparison with the current study (Steagall et al. 2006). In the authors' experience, the doses reported here are commonly used during general anesthesia in the canine patient. ISO-sparing effects could have been greater with higher doses of fentanyl, or if used in high-risk patients, or when other anesthetics or analgesics are combined (Ilkiw et al. 1993).

Dexmedetomidine is the most selective alpha$_2$ agonist that is commonly used in small animal anesthesia because of its sedative, anxiolytic and analgesic effects (Khan et al. 1999a; Lin et al. 2008; Uilenreef et al. 2008). It is also used to reduce the dose rates of other anesthetic agents administered for induction and maintenance of general anesthesia (Khan et al. 1999b; Uilenreef et al. 2008). In the present study, DEX decreased F_E'Iso by a similar magnitude previously measured in dogs (Pascoe et al. 2006; Campagnol et al. 2007; Uilenreef et al. 2008). However, it is clear that ISO-sparing effects were not as great as previously demonstrated (Pascoe et al. 2006; Campagnol et al. 2007; Uilenreef et al. 2008). This may have been related to the doses employed here, but also because comparisons were made with a control group receiving butorphanol; an agonist at k (OP1) and antagonist at μ (OP3) opioid receptors that has been shown to decrease the MAC_{ISO} by 20.3 ± 12.9% (Ko et al. 2000).

Alpha$_2$ agonists have been documented to produce transient hyperglycemia resulting from alpha$_2$-receptor-mediated inhibition of insulin release from beta cells (Khan et al. 1999a; Pawson 2008) and, therefore, it was not surprising that glucose concentrations were higher in groups LKD and DEX.

Lidocaine is an amide local anesthetic that has been used as an adjunct of general anesthesia in dogs (Valverde et al. 2004; Wilson et al. 2008). It reduces the MAC of volatile anesthetics in a dose-dependent manner, and without significant cardiovascular changes (Valverde et al. 2004; Wilson et al. 2008). When LIDO was administered to dogs (loading dose of 2 mg kg^{-1} followed by a CRI of 50 μg kg^{-1} minute^{-1}), it decreased MAC$_{ISO}$ by 18.7% (Valverde et al. 2004), whereas a 29% reduction was obtained at the same CRI dose even without a loading dose (Muir et al. 2003). In the present study, a reduction of 22.5% (range, 16.8 to 28.3%) in ISO requirement was recorded after a loading dose of 2 mg kg^{-1} followed by a CRI of 100 μg kg^{-1} minute^{-1} which was quite similar to the MAC studies (Muir et al. 2003; Valverde et al. 2004).

Ketamine is a dissociative anesthetic agent with N-methyl-D-aspartate (NMDA) antagonistic properties that has been used to produce ISO-sparing effects and postoperative analgesia (Wagner et al. 2002). It has been demonstrated that a KET CRI reduces the MAC$_{ISO}$ in a dose-dependent fashion (Muir et al. 2003; Solano et al. 2006; Wilson et al. 2008). In the absence of a loading dose, a 10 μg kg^{-1} minute^{-1} dose of ketamine reduced the MAC$_{ISO}$ by 25% (Muir et al. 2003). Another study using target-controlled infusion documented MAC$_{ISO}$ reduction from 10.9 to 39.5% in dogs (Solano et al. 2006), similar to the 12.7 to 28.9% reduction in FE′Iso in this study. Since lidocaine and ketamine have been shown to produce a dose-dependent reduction in MAC$_{ISO}$ (Valverde et al. 2004; Solano et al. 2006), it is clear that higher doses of both drugs could have produced greater ISO-sparing effects. This study could not demonstrate that a significant reduction in ISO requirements in LIDO or KET was associated with a significantly higher blood pressure during surgery when compared with CONTROL/BUT. Lidocaine and ketamine CRIs may provide other benefits like sedation, analgesia or antihyperalgesia in dogs undergoing surgery that the current study design was not able to demonstrate. In addition, recovery times were shorter in these groups when compared with FENT, DEX and/or LKD.

To the authors' knowledge there is no published data about the use of LKD in dogs. In the study presented here, the combination LKD resulted in greater ISO-sparing effects than LIDO, KET and DEX, although to a lesser extent than the sum of the three treatments. An additive effect may result from this protocol due to their different mechanisms of action in the nociceptive pathway (Hendrickx et al. 2008). LIDO is a typical sodium channel blocker that reduces the inhalant MAC by means of its sedative and analgesics effects due to unclear mechanisms (Frölich et al. 2010). Ketamine is a dissociative anesthetic and NMDA receptor antagonist that may prevent central sensitization, opioid-induced hyperalgesia, dependence and tolerance from occurring (Pozzi et al. 2006). Dexmedetomidine is an alpha$_2$ adrenoreceptor agonist that induces sedation and analgesia by activation of alpha$_2$ adrenoreceptors in the central nervous system and in the dorsal horn of the spinal cord (Murrell & Hellebrekers 2005). This may explain the profound reduction in FE′Iso (54.9% and 35.3–59.5%, mean and range, respectively) after LKD in comparison with CONTROL/BUT, KET, LIDO, and at some time points, with DEX. This combination may be useful where opioids are unavailable, however the cardiovascular effects after LKD were similar to DEX. Recovery times (time to extubation, time to first head lift, time to sternal recumbency and time to standing) were longer in DEX and LKD than in other treated groups. In the clinical setting, this may be prevented by the administration of an alpha$_2$ adrenoreceptor antagonist to antagonize the sedative and cardiovascular effects of dexmedetomidine.

With the exception of LKD and LIDO, there was a significant HR increase at T2 in all groups when compared with baseline. This could be due to intense surgical stimulation and autonomic nervous system activation when traction and ligation of the ovaries were performed. The CONTROL/BUT required the highest concentrations of ISO to suppress such stimulus, accompanied by decreases in arterial blood pressure most likely mediated by isoflurane-induced vasodilation. This study confirmed that the addition of other anesthetic agents administered by CRI decreased FE′Iso and was accompanied by varying degrees of increased arterial blood pressure.

Conclusion and clinical relevance

At the doses administered, FENT and LKD resulted in greater ISO-sparing effect than did LIDO, KET or

CONTROL/BUT, although this was not observed at all time points. It appeared that the low HR induced by FENT may have contributed to lower arterial pressure than expected from reduced F_E'Iso.

Acknowledgements

Eduardo Gutierrez-Blanco was sponsored by a scholarship provided by SEP-PROMEP.

References

Aguado D, Benito J, Gómez de Segura IA (2011) Reduction of the minimum alveolar concentration of isoflurane in dogs using a constant rate of infusion of lidocaine–ketamine in combination with either morphine or fentanyl. Vet J 189, 63–66.

Camargo JB, Steagall PV, Minto BW et al. (2011) Postoperative analgesic effects of butorphanol or firocoxib administered to dogs undergoing elective ovariohysterectomy. Vet Anaesth Analg 38, 252–259.

Campagnol D, Teixeira FJ, Giordano T et al. (2007) Effects of epidural administration of dexmedetomidine on the minimum alveolar concentration of isoflurane in dogs. Am J Vet Res 68, 1310–1318.

Columbano N, Secci F, Careddu GM et al. (2012) Effects of lidocaine constant rate infusion on sevoflurane requirement, autonomic responses, and postoperative analgesia in dogs undergoing ovariectomy under opioid-based balanced anesthesia. Vet J 193, 448–455.

Congdon JM, Marquez M, Niyom S et al. (2013) Cardiovascular, respiratory, electrolyte and acid-base balance during continuous dexmedetomidine infusion in anesthetized dogs. Vet Anaesth Analg 40, 464–471.

Doherty T, Redua MA, Queiroz-Castro P et al. (2007) Effect of intravenous lidocaine and ketamine on the minimum alveolar concentration of isoflurane in goats. Vet Anaesth Analg 34, 125–131.

Dyson DH, James-Davies R (1999) Dose effect and benefits of glycopyrrolate in the treatment of bradycardia in anesthetized dogs. Can Vet J 40, 327–331.

Frölich MA, McKeown JL, Worrell MJ et al. (2010) Intravenous lidocaine reduces ischemic pain in healthy volunteers. Reg Anesth Pain Med 35, 249–254.

Hendrickx JFA, Eger EI, Sonner JM et al. (2008) Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg 107, 494–506.

Ilkiw JE, Pascoe PJ, Haskins SC et al. (1993) The cardiovascular sparing effect of fentanyl and atropine, administered to enflurane anesthetized dogs. Can J Vet Res 57, 248–253.

Khan ZP, Ferguson CN, Jones RM (1999a) Alpha-2 and imidazoline receptor agonist. Their pharmacology and therapeutic role. Anaesthesia 54, 146–165.

Khan ZP, Munday IT, Jones RM et al. (1999b) Effects of dexmedetomidine on isoflurane requirements in healthy volunteers 1: pharmacodynamic and pharmacokinetic interactions. Br J Anaesth 83, 372–380.

Ko JC, Lange DN, Mandsager RE et al. (2000) Effects of butorphanol and carprofen on the minimal alveolar concentration of isoflurane in dogs. J Am Vet Med Assoc 217, 1025–1028.

Lin G, Robben JH, Murrell JC et al. (2008) Dexmedetomidine constant rate infusion for 24 hours during and after propofol or isoflurane anaesthesia in dogs. Vet Anaesth Analg 35, 141–153.

Matsubara LM, Oliva VNLS, Gabas D et al. (2009) Effect of lidocaine on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg 36, 407–413.

Muir WW, Wiese AJ, March PA (2003) Effects of morphine, ketamine and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. Am J Vet Res 64, 1155–1160.

Murrell JC, Hellebrekers LJ (2005) Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth Analg 32, 117–127.

Ortega M, Cruz I (2011) Evaluation of a constant rate infusion of lidocaine for balanced anesthesia in dogs undergoing surgery. Can Vet J 52, 856–860.

Pascoe PJ, Raekallio M, Kuusela E et al. (2006) Changes in the MAC of isoflurane and some cardiopulmonary measurements during three continuous infusion rates of dexmedetomidine in dogs. Vet Anaesth Analg 33, 97–103.

Pawson P (2008) Sedatives. In: Small Animal Clinical Pharmacology (2nd edn). Maddison J, Page S, Church D (eds). Saunders (Elsevier), UK, pp. 113–125.

Pozzi A, Muir WW, Traverso F (2006) Prevention of central sensitization and pain by N-methyl-D-aspartate receptor antagonist. J Am Vet Med Assoc 228, 53–60.

Sano T, Nishimura R, Kanazawa H et al. (2006) Pharmacokinetics of fentanyl after single intravenous injection and constant rate infusion in dogs. Vet Anaesth Analg 33, 266–273.

Solano AM, Pypendop BH, Boscan PL et al. (2006) Effect of intravenous administration of ketamine on the minimum alveolar concentration of isoflurane in anesthetized dogs. Am J Vet Res 67, 21–25.

Steagall PVM, Teixeira FJ, Minto BW et al. (2006) Evaluation of the isoflurane-sparing effects of lidocaine and fentanyl during surgery in dogs. J Am Vet Med Assoc 229, 522–527.

Steffey EP, Howland D (1977) Isoflurane potency in the dog and cat. Am J Vet Res 38, 1833–1849.

Ueyama Y, Lerche P, Eppler M et al. (2009) Effects of intravenous administration of perzinfotel, fentanyl, and a combination of both drugs on the minimum alveolar

concentration of isoflurane in dogs. Am J Vet Res 70, 1459–1464.

Uilenreef JJ, Murrell JC, McKusick B et al. (2008) Dexmedetomidine continuous rate infusion during isoflurane anaesthesia in canine surgical patients. Vet Anaesth Analg 35, 1–12.

Valverde A, Doherty TJ, Hernández J et al. (2004) Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg 31, 264–271.

Wagner AE, Walton JA, Hellyer PW et al. (2002) Use of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. J Am Vet Med Assoc 221, 72–75.

Wilson J, Doherty TJ, Egger CM et al. (2008) Effects of intravenous lidocaine, ketamine, and the combination on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg 35, 289–296.

Received 15 August 2012; accepted 6 November 2012.