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RESEARCH PAPER

General anesthesia with an injectable 8% v/v sevoflurane lipid emulsion administered intravenously to dogs

Claudio C Natalini*, Priscila B Da Silva Serpa†, Ruben L Cavalcanti†, Alexandre S Polydoro†, Joanna E Griffith*, Luiz CP Santos* & Anthony Nicholson*

*Companion Animal Health Centre, School of Animal and Veterinary Sciences, The University of Adelaide, Roseworthy, SA, Australia

†Postgraduate Program in Animal Medicine, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil

Correspondence: Claudio C Natalini, Postgraduate Program in Animal Medicine PPGAME, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. E-mail: ccnatalini@outlook.com

Abstract

Objective To evaluate the potential of an intravenous (IV) sevoflurane formulation for maintenance of general anesthesia in dogs.

Study design Prospective crossover design.

Animals Six healthy, mature, mixed-breed dogs, four males and two females, weighing 11.7 ± 3.4 kg.

Methods Anesthesia was induced and maintained with propofol IV for instrumentation. Baseline measurements were recorded before administration of either sevoflurane in oxygen (Sevo-Inh) or lipid-emulsified sevoflurane 8% v/v in 30% Intralipid IV (Sevo-E), 0.5 mL kg^{-1} over 5 minutes followed by an infusion at 0.1–0.3 mL kg^{-1} $minute^{-1}$. Dogs were breathing spontaneously. The 'up-and-down' technique was used to determine the minimum alveolar concentration (MAC) of sevoflurane. Over 120 minutes, a tail clamp was applied every 15 minutes and sevoflurane administration was adjusted depending on the response. End-tidal sevoflurane concentration and variables were recorded at 30, 60, 90, and 120 minutes: heart rate (HR), systemic arterial pressure (sAP), respiratory rate (f_R), end-tidal carbon dioxide tension, hemoglobin oxygen saturation (SaO_2), arterial pH and blood gases, blood urea nitrogen, alanine aminotransferase, creatine kinase, gamma-glutamyl transferase, and aspartate aminotransferase.

Results There were no significant differences between treatments for HR, sAP, f_R, SaO_2, and biochemical variables ($p > 0.05$). pH and HCO_3^- were significantly decreased, and $PaCO_2$ increased from baseline in Sevo-E ($p < 0.05$). MAC was significantly lower for Sevo-E than for Sevo-Inh, although the required dose of sevoflurane (g $hour^{-1}$) to maintain general anesthesia was not significantly different between treatments.

Conclusions and clinical relevance Administration of 8% v/v sevoflurane lipid emulsion IV was effective in maintaining general anesthesia in dogs, but resulted in moderate cardiopulmonary depression, metabolic and respiratory acidosis. The amount of sevoflurane (g $hour^{-1}$) required to maintain general anesthesia was significantly lower for inhaled than for IV sevoflurane.

Keywords canine, hemodynamics, lipid emulsion, sevoflurane.

Introduction

The development of emulsified halogenated anesthetic agents to be administered intravenously (IV) as an alternative to inhalation anesthesia is a rapidly

developing area of anesthesia with the potential to revolutionize anesthetic delivery (Johnson et al. 2011; Jee et al. 2012). Recent studies have shown the capability of injectable halogenated anesthetics to protect organs such as the brain, heart, and kidneys (Zaugg et al. 2003; Chiari et al. 2004; Fukazawa & Lee 2014). Intravenous emulsified isoflurane, enflurane, and sevoflurane produce acute and delayed preconditioning against myocardial infarction after a coronary occlusion in rabbits (Chiari et al. 2004). Clinically used, inhaled halogenated anesthetics induce potent anti-inflammatory, antinecrotic, and antiapoptotic effects that protect against acute kidney injury (Fukazawa & Lee 2014). In theory, another advantage of administering halogenated anesthetic IV over traditional inhalational delivery would be to decrease the amount of drug necessary to produce general anesthesia (Yang et al. 2006).

The proposed mechanisms for cell and tissue protection involve activation of mitochondrial G-protein receptors leading to ATP production that prevents cellular apoptosis, and also prevents an increase in cytosolic mitochondrial Ca^{2+} concentration and high metabolic mitochondrial activity in both early protection (1–3 hours) and delayed protection (12–72 hours) (Zaugg et al. 2003).

Complications of IV injection of liquid inhalation anesthetics have included lung injury with acute respiratory failure, cardiovascular instability, pulmonary damage, and hemorrhage (Biber et al. 1984; Kawamoto et al. 1992; Musser et al. 1999; Krahn et al. 2012). Vehicles that have been investigated to deliver halogenated anesthetics IV are Intralipid and fluorocarbon-based emulsions (Johnson et al. 2011; Jee et al. 2012; Zhou & Liu 2012).

The median effective dose (ED50) and the median lethal dose (LD50) for IV sevoflurane lipid emulsion have been reported in mice but not in dogs (Eger & MacLeod 1995). These are values that should be known in order to establish a therapeutic index for lipid-emulsified sevoflurane. The anesthetic and physiologic effects of IV lipid-emulsified halothane in swine and dogs, and of lipid-emulsified isoflurane in dogs have been reported (Musser et al. 1999; Yang et al. 2013). None of these studies compared the dose rates of inhaled and injectable halogenated agents necessary to maintain general anesthesia.

In dogs, the minimum alveolar concentration (MAC) of an IV infusion of lipid-emulsified isoflurane (8% v/v) was determined to be $1.12 \pm 0.18\%$, significantly less than the MAC measured during inhalation of isoflurane ($1.38 \pm 0.16\%$) (Yang et al. 2006). The MAC of an IV infusion (MAC_{IV}) of lipid-emulsified sevoflurane has not been published. It is expected that MAC_{IV} for sevoflurane will be lower than the inhaled MAC, similar to isoflurane. Administration of sevoflurane fluorous emulsion or fluorocarbon-based nanoemulsion results in a fast induction of anesthesia with a loss of righting reflex in about 20 seconds in rats, followed by a rapid recovery. The rapid pharmacokinetic profile after a single IV injection could be caused by quick sevoflurane release from the emulsion and the rapid recovery due to redistribution and elimination of the anesthetic through the lungs (Johnson et al. 2011; Jee et al. 2012).

Approximately 5% of absorbed sevoflurane is metabolized by cytochrome P450 2E1 to hexafluoroisopropanol (HFIP), with the release of inorganic fluoride and CO_2. Sevoflurane is not metabolized to trifluoroacetic acid (Frink et al. 1994; Kharasch et al. 1996; Tanaka et al. 2000). This may provide significant advantages, because trifluoroacetic acid is an extremely strong acid, 34,000-fold stronger than acetic acid (Milne & Parker 1981) and may contribute to severe acute metabolic acidosis during anesthesia.

Serum activity of the enzymes aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, alkaline phosphatase, and gamma-glutamyl transferase (GGT), and the concentration of total bilirubin have been used as biochemical indicators of hepatobiliary function in dogs. Studies have shown significant increases in activity of these enzymes, and an increase in the serum concentration of total bilirubin after inhaled isoflurane or sevoflurane anesthesia in dogs at clinical concentrations (Yuan et al. 2012).

The goal of the present study was to evaluate the effects of IV administration of a continuous rate infusion (CRI) of 8% sevoflurane in 30% lipid emulsion on cardiovascular variables, acid-base balance, and renal and hepatic function when compared with inhaled sevoflurane anesthesia in dogs. The hypothesis was that the amount of sevoflurane (in g $hour^{-1}$) required to maintain general anesthesia would be lower with IV administered 8% lipid-emulsified sevoflurane than with inhaled sevoflurane.

Material and methods

Approval was obtained from the Institutional Animal Care and Use Committee of Hospital de Clinicas

de Porto Alegre, Brazil (CEUA/HCPA – protocol no. 08-675).

Anesthetic agents

Sevoflurane (Sevocris sevoflurane 99.99%) (CAS: 28523-86-6) was obtained from Cristália Produtos Químicos e Farmacêuticos, Ltda., Brazil. Intralipid (30%) was purchased from Baxter International Inc., IL, USA. Sevoflurane emulsion was prepared as previously described for lipid-emulsified isoflurane (Kawamoto et al. 1992). In order to prepare the 8% v/v sevoflurane lipid emulsion, 1.6 mL of liquid 7.6 M sevoflurane was injected into a sealed sterile vial containing 18.4 mL of 30% Intralipid. Vials were placed in an orbital shaker at 1.43 ***g*** for 10 minutes (KS 130; IKA, Malaysia). A total of 80 vials were produced and stored refrigerated at 4–6 °C from 30 to 90 days before use. Stability and sterility tests were performed by a commercial company (Cristália Produtos Químicos e Farmacêuticos, Ltda.) before experimental use. Particle size for the lipid emulsion was not determined.

Study design

Six healthy, mature, mixed-breed dogs, four males and two females, weighing mean ± standard deviation (SD) 11.7 ± 3.4 kg, were studied.

Animals had a 20 gauge catheter aseptically inserted in one of the cephalic veins. Propofol was administered (4–6 mg kg^{-1}; Diprivan; Fresenius Kabi, IL, USA) IV to effect for induction of anesthesia and orotracheal intubation. Boluses of propofol (1–2 mg kg^{-1}) IV were used to maintain anesthesia for instrumentation, if needed. All dogs were placed in right lateral recumbency and connected to a circle anesthetic delivery system with an oxygen flow rate of 1.0 L $minute^{-1}$ and were allowed to breathe spontaneously. Lactated Ringer's solution (10 mL kg^{-1} $hour^{-1}$) was administered IV during anesthesia.

Animal instrumentation

Instrumentation consisted of catheterization of the left jugular vein with an 18 gauge, 47.6 mm catheter (Abbott Laboratories, IL, USA), one of the cephalic veins with a 20 gauge, 31.8 mm catheter (Abbott Laboratories), and a dorsal pedal artery with a 22 gauge, 19 mm catheter (Abbott Laboratories), in order to collect venous blood samples for biochemical analyses and to measure arterial blood pressure and collect arterial blood samples for blood gas analysis. All monitors and biochemical equipment were calibrated weekly by the medical engineer division of the Hospital de Clinicas de Porto Alegre (HCPA).

After instrumentation, general anesthesia was maintained with sevoflurane by inhalation (Sevo-Inh treatment) or by IV administration of lipid-emulsified sevoflurane (Sevo-E treatment). All Sevo-Inh experiments were completed before the Sevo-E experiments, which were performed 7 days later. Dogs were not randomly assigned to the treatments in the event that the lipid-emulsified sevoflurane produced allergic or anaphylactic reactions. The anesthetic period with inhaled or injectable sevoflurane lasted for 120 minutes after the baseline data were collected.

Physiologic and biochemical variables

Heart rate (HR) was recorded from the electrocardiogram, respiratory rate (f_R) was obtained using a spirometer, and systolic, diastolic and mean arterial pressures (SAP, DAP, and MAP, respectively) were measured from the dorsal pedal artery catheter (DTX Plus; Argon Critical Care Systems Singapore PTE Ltd., Singapore). The transducer was connected to the arterial catheter through noncompliant tubing (Microbore extension set; Multigate Medical Devices, Germany) and placed as close as possible to the level of dog's heart using the manubrium as reference. The arterial catheter was flushed with heparinized 0.9% saline (10 U mL^{-1}) as necessary to observe an appropriate pulse wave and 2–5 minutes before blood sample collection. End-tidal carbon dioxide partial pressure ($P_{E'}CO_2$) and expired sevoflurane concentration ($F_{E'}$Sevo) were monitored through a side-stream sensor connected to a port at the junction of the endotracheal tube and the Y piece, with a sampling aspiration flow rate of 200 ± 20 mL $minute^{-1}$. A pulse oximetry (SpO_2) ear lobe probe was placed on the tongue (Datex Ohmeda TruStat Datex-Ohmeda; GE Medical Systems, WI, USA). A multiparametric monitor (S/5 Datex-Ohmeda) was calibrated prior to the start of the study and weekly by the HCPA medical engineering division. Variables were recorded during propofol anesthesia before administration of sevoflurane (baseline) and then every 30 minutes for 120 minutes during the MAC determination. Variables were recorded after measurement of $F_{E'}$Sevo but before application of a noxious stimulus.

Venous blood samples were also collected to obtain serum concentrations of ALT, AST, GGT, creatine kinase (CK), and blood urea nitrogen (BUN) measured by the UV-kinetic method (Modular P; Roche Diagnostics, Germany). Arterial blood was collected for analysis of pH, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), standard bicarbonate (HCO_3^-), and arterial hemoglobin oxygen saturation (SaO_2) (RapidLab 865; Bayer Diagnostics, PA, USA).

Minimum alveolar concentration determination

The study was conducted at 21 °C room temperature and 761 mmHg barometric pressure. The anesthetic depth was determined by the absence of palpebral reflex and ventromedial rotation of the eyes after propofol induction and during sevoflurane administration.

In Sevo-Inh, Fe′Sevo was initially maintained at 2.3% for 15 minutes with an oxygen flow rate of 1 L minute^{-1} and by adjusting the measured flow vaporizer (Multi-agent measured flow vaporizer; K. Takaoka, Brazil). Fe′Sevo was determined using an anesthetic gas module (S/5 Datex-Ohmeda; GE Medical Systems).

In Sevo-E, sevoflurane lipid emulsion was administered as a CRI with a syringe pump (LF Inject; Lifemed, Brazil). After a bolus injection of 0.5 mL kg^{-1} over 5 minutes, anesthesia was maintained by adjusting the syringe pump to deliver 0.1 mL kg^{-1} minute^{-1} up to 0.3 mL kg^{-1} minute^{-1} (6–18 mL kg^{-1} hour^{-1}). Initially, Fe′Sevo was maintained at 1.0% for 15 minutes and then the infusion was adjusted according to the dog's responses to a noxious stimulus.

The 'up-and-down' technique was used to determine the MACs in the Sevo-Inh (MAC_{Inh}) and Sevo-E (MAC_{IV}) treatments as previously described (Yang et al. 2006). The tail-clamp technique was used as a noxious stimulus (full-length Rochester-Carmalt 22 cm hemostat applied close to the base of the tail and clamped to full ratchet lock for a maximum of 10 seconds) and was delivered at 15 minute intervals for 120 minutes. If there was no response to stimulation, the Fe′Sevo was lowered to 80% of the preceding concentration and the stimulus repeated after allowing 15 minutes for equilibration. If a positive response to stimulation (purposeful movement) was obtained, the Fe′Sevo was increased by 20% and 15 minutes allowed for equilibration. Fe′Sevo determination was done in duplicate in order to check for consistency in MAC determination. The anesthetic concentration midway between the highest allowing movement and the lowest preventing movement was considered to represent the MAC. The observer responsible for MAC determinations (CCN) was unaware of treatment allocation.

Statistical analysis

All results were expressed as means ± SD. The data were evaluated by two-way repeated-measures anova. Bonferroni and Student–Newman–Keuls (SNK) *post hoc* test for multiple comparisons were applied for significant variables at $p < 0.05$.

Sample size was calculated considering an alpha level of 0.05 and a power of 0.80 for an estimated SD of 0.5% and a minimum difference of 1% for Fe′Sevo between treatments (Steel & Torrie 1980).

Results

Fe′Sevo and MAC

There was a highly significant difference in Fe′Sevo between Sevo-Inh and Sevo-E ($p < 0.001$) (Table 1). The Fe′Sevo necessary to maintain the MAC (MAC_{Inh}) in the Sevo-Inh treatment varied between 2.32 ± 0.08% and 2.35 ± 0.10%, while for the Sevo-E treatment, Fe′Sevo ranged from 0.40 ± 0.08% to 0.79 ± 0.35% (MAC_{IV}).

Sevoflurane emulsion infusion and dosage rates

For the 8% v/v Sevo-E treatment, the infusion rate was maintained at 0.3 mL kg^{-1} minute^{-1}, which corresponds to 0.024 mL kg^{-1} minute^{-1} (1.44 mL kg^{-1} hour^{-1}) of liquid sevoflurane. The mean dosage rate was significantly lower for Sevo-E than for Sevo-Inh. Sevoflurane dosage was 13.1 g hour^{-1} in Sevo-Inh and 25.4 g hour^{-1} in Sevo-E. For the Sevo-Inh treatment, dose calculation was done by multiplying the amount of liquid sevoflurane hour^{-1} (in mL, 8.65) necessary to maintain general anesthesia by 1.52 g (7.6 m sevoflurane density at 21 °C).

HR, SpO_2, and blood pressure

Hemodynamic variables were not significantly different between treatments during the study times. Arterial blood pressures were not different between treatments. HR and SpO_2 were not significantly

Table 1 Cardiopulmonary variables (mean ± standard deviation) measured during propofol anesthesia (baseline) and at 30 minute intervals for 120 minutes during administration of inhaled sevoflurane (Sevo-Inh) and intravenous sevoflurane emulsion (Sevo-E) in six dogs

		Sevoflurane anesthesia (minutes)			
Variable/treatment	**Propofol anesthesia (baseline)**	**30**	**60**	**90**	**120**
HR (beats minute^{-1})					
Sevo-Inh	115 ± 15	97 ± 2	113 ± 13	97 ± 2	98 ± 2
Sevo-E	104 ± 11	98 ± 5	98 ± 2	107 ± 14	101 ± 10
SAP (mmHg)					
Sevo-Inh	105 ± 25	97 ± 10	95 ± 16	94 ± 4	91 ± 13
Sevo-E	96 ± 26	93 ± 27	93 ± 31	86 ± 28	92 ± 33
MAP (mmHg)					
Sevo-Inh	85 ± 16	68 ± 7	65 ± 13	69 ± 8	59 ± 6
Sevo-E	66 ± 18	66 ± 17	62 ± 21	62 ± 17	59 ± 17
DAP (mmHg)					
Sevo-Inh	76 ± 11	54 ± 5	50 ± 12	57 ± 7	43 ± 3
Sevo-E	70 ± 14	52 ± 12	47 ± 16	50 ± 11	43 ± 10
f_R (breaths minute^{-1})					
Sevo-Inh	14 ± 3	16 ± 2	15 ± 2	16 ± 1	16 ± 1
Sevo-E	22 ± 8	18 ± 3	14 ± 5*	16 ± 3*	15 ± 3*
$P_{E'}CO_2$ (mmHg) (kPa)					
Sevo-Inh	35 ± 2 (4.7 ± 0.3)	46 ± 3 (6.1 ± 0.4)	39 ± 4 (5.2 ± 0.5)	41 ± 7 (5.5 ± 1.0)	41 ± 5 (5.5 ± 0.7)
Sevo-E	32 ± 10 (4.2 ± 1.3)	39 ± 8 (5.2 ± 1.0)	37 ± 6 (4.9 ± 0.8)	41 ± 5 (5.5 ± 0.7)	38 ± 6 (4.9 ± 0.8)
$PaCO_2$ (mmHg) (kPa)					
Sevo-Inh	45 ± 2 (6.0 ± 0.2)	42 ± 1 (5.6 ± 0.1)	40 ± 2 (5.3 ± 0.2)	42 ± 1 (5.6 ± 0.1)	43 ± 1 (5.7 ± 0.1)
Sevo-E	42 ± 6 (5.6 ± 0.8)	54 ± 12* (7.2 ± 1.6)	54 ± 13* (7.2 ± 1.7)	52 ± 12* (6.9 ± 1.5)	50 ± 15* (6.7 ± 1.9)
HCO_3^- (mEq L^{-1})					
Sevo-Inh	22.6 ± 0.8	23.3 ± 0.5	23.0 ± 0.7	22.9 ± 0.6	22.8 ± 0.6
Sevo-E	25.8 ± 1.4	19.3 ± 3.4*	21.7 ± 3.1*	21.4 ± 1.3*	20.6 ± 1.2*
Base excess (mEq L^{-1})					
Sevo-Inh	–3.6 ± 0.6	–1.7 ± 0.9	–2.1 ± 0.6	–2.5 ± 0.3	–2.5 ± 0.3
Sevo-E	–1.3 ± 0.5	–9.4 ± 3.6*	–6.4 ± 2.8	–6.2 ± 1.3	–6.7 ± 2.9
pH					
Sevo-Inh	7.32 ± 0.01	7.37 ± 0.01	7.36 ± 0.06	7.35 ± 0.01	7.35 ± 0.01
Sevo-E	7.31 ± 0.02	7.17 ± 0.08*	7.23 ± 0.08*	7.24 ± 0.08*	7.23 ± 0.1*

(continued)

Table 1 (continued)

Variable/treatment	Propofol anesthesia (baseline)	Sevoflurane anesthesia (minutes)			
		30	60	90	120
$SpO_{2\%}$					
Sevo-Inh	98 ± 2	97 ± 2	97 ± 2	97 ± 2	99 ± 2
Sevo-E	97 ± 2	95 ± 1	97 ± 3	97 ± 2	97 ± 3
PaO_2 (mmHg) (kPa)					
Sevo-Inh	438 ± 59 (58 ± 8)	453 ± 90 (60 ± 12)	467 ± 86 (62 ± 12)	476 ± 120 (63 ± 16)	405 ± 126 (54 ± 17)
Sevo-E	504 ± 39 (67 ± 5)	562 ± 30 (75 ± 4)	535 ± 31 (71 ± 4)	534 ± 54 (71 ± 7)	550 ± 28 (73 ± 4)
SaO_2 (%)					
Sevo-Inh	99 ± 2	99 ± 2	99 ± 3	98 ± 2	99 ± 3
Sevo-E	99 ± 0	99 ± 1	99 ± 1	99 ± 1	99 ± 2
$F_{E'}$Sevo (%)					
Sevo-Inh		2.35 ± 0.06	2.32 ± 0.08	2.32 ± 0.08	2.35 ± 0.10
Sevo-E		0.61 ± 0.20†	0.67 ± 0.10†	0.62 ± 0.30†	0.52 ± 0.20†
FISevo (%)					
Sevo-Inh		2.35 ± 0.40	2.32 ± 0.40	2.35 ± 0.90	2.35 ± 0.90
Sevo-E		0.09 ± 0.10†	0.09 ± 0.02†	0.09 ± 0.02†	0.09 ± 0.02†

HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; f_R, respiratory rate; $P_{E'}CO_2$, end-tidal carbon dioxide tension; $PaCO_2$, arterial partial pressure of CO_2; HCO_3^-, standard bicarbonate; SpO_2, peripheral hemoglobin oxygen saturation; SaO_2, arterial hemoglobin oxygen saturation; $F_{E'}$Sevo, end-tidal sevoflurane; FISevo, inspired sevoflurane. *Significantly different from baseline ($p < 0.05$). †Significantly different between Sevo-E and Sevo-Inh treatments ($p < 0.001$).

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different from baseline or between treatments (Table 1).

f_R and arterial blood gases

The value f_R was not significantly different between treatments throughout the study time, but decreased significantly from baseline in Sevo-E (Table 1). $PaCO_2$ was significantly increased from baseline in Sevo-E. pH and HCO_3^- were significantly decreased in Sevo-E from 30 to 120 minutes when compared with baseline values ($p < 0.05$) (Table 1). Base excess (BE) was decreased at 30 minutes but there was no significant difference between treatments. PaO_2 and SaO_2 were not significantly different from baseline or between treatments (Table 1).

Biochemical variables

No significant differences in ALT, AST, GGT, CK, and BUN were observed from baseline or between treatments (Table 2).

Recovery from anesthesia

Mild facial edema, including perioral and periocular tissues, was observed in all animals after 30 minutes of infusion in the Sevo-E treatment. Facial edema spontaneously disappeared within 120 minutes from the end of emulsion administration.

All dogs recovered without further complications after the study. The dogs were extubated within 20 minutes from the end of sevoflurane administration. All dogs were observed for further complications, and HR, sAP, f_R and body temperature were monitored up to 24 hours after the study was finished. No adverse effects were observed.

Discussion

Others have proposed that an emulsified inhaled halogenated anesthetic administered IV would result in a lower consumption of the agent compared with administration by inhalation (Yang et al. 2006, 2013; Krahn et al. 2012). Emulsified halogenated inhaled anesthetics administered IV are partially excreted through the lungs, with the remaining drug being metabolized in the liver before renal excretion (Lucchinetti et al. 2008). In this study, the FE′Sevo in the Sevo-E treatment was significantly lower than that in the Sevo-Inh treatment. A similar difference has been described in the comparison of isoflurane-loaded lipid emulsion or nanoemulsions and inhaled isoflurane (Yang et al. 2006; Krahn et al. 2012). The end-tidal anesthetic concentration was significantly lower for the emulsified sevoflurane, but the difference does not reflect the actual amount of drug necessary to maintain general anesthesia, as the injectable emulsified form is only partially excreted through the lungs. In the present study, the amount

Table 2 Biochemical variables (mean ± standard deviation) measured during propofol anesthesia (baseline) and at 30 minute intervals for 120 minutes during administration of inhaled sevoflurane (Sevo-Inh) or intravenous sevoflurane emulsion (Sevo-E) in six dogs

Variables/ treatment	Propofol anesthesia (baseline)	Sevoflurane anesthesia (minutes)			
		30	60	90	120
BUN (mg dL^{-1})					
Sevo-Inh	35 ± 11	33 ± 9	33 ± 9	32 ± 7	38 ± 22
Sevo-E	39 ± 24	36 ± 23	38 ± 23	39 ± 23	32 ± 7
ALT (U L^{-1})					
Sevo-Inh	25 ± 4	28 ± 12	29 ± 12	30 ± 12	31 ± 13
Sevo-E	25 ± 6	22 ± 10	22 ± 10	22 ± 9	22 ± 10
CK (U L^{-1})					
Sevo-Inh	99 ± 10	97 ± 10	96 ± 13	87 ± 16	216 ± 107
Sevo-E	142 ± 55	78 ± 21	92 ± 17	120 ± 36	91 ± 19
GGT (U L^{-1})					
Sevo-Inh	3.2 ± 0.3	3.1 ± 0.4	3.1 ± 0.4	3.1 ± 0.4	3.2 ± 0.2
Sevo-E	3.3 ± 0.3	3.2 ± 0.3	3.4 ± 0.4	3.4 ± 0.3	3.1 ± 0.2
AST (U L^{-1})					
Sevo-Inh	23 ± 2	21 ± 3	18 ± 6	18 ± 5	19 ± 5
Sevo-E	18 ± 5	17 ± 5	17 ± 5	17 ± 4	18 ± 4

BUN, blood urea nitrogen; ALT, alanine transaminase; CK, creatine kinase; GGT, gamma glutamyltransferase; AST, aspartate transaminase.

(g $hour^{-1}$) of sevoflurane required for maintenance of general anesthesia was significantly lower for the inhaled sevoflurane than for the IV-administered 8% (v/v) lipid-emulsified sevoflurane. In spite of a significant difference between inhaled and injectable sevoflurane MAC values shown in this study, it is possible that the difference in dosage (g $hour^{-1}$) was due to increased tissue solubility of the lipid-emulsified sevoflurane, as described for isoflurane in other studies (Yang et al. 2006). The higher tissue solubility of lipid-emulsified injectable sevoflurane could have decreased its availability for pulmonary excretion, and consequently lowered the Fe′Sevo.

Halogenated anesthetics have been shown to acutely protect the myocardium against irreversible ischemic injury. This anesthetic ischemic preconditioning (IPC) has been investigated intensively by several investigators, who have demonstrated that both the inhaled form and the injectable emulsified halogenated forms have protective effects (Chiari et al. 2004; Lucchinetti et al. 2008). The mechanisms for anesthetic-induced myocardial protection are similar to those observed during IPC and are mediated by K_{ATP} channels, A_1 receptors and protein kinase C2 (Lee et al. 2004). Studies have demonstrated that less soluble halogenated anesthetics are less potent in providing renal protection when compared with more soluble inhaled anesthetics (Fukazawa & Lee 2014). When inhaled, the solubility of sevoflurane in brain, kidney, and liver is no different from that of isoflurane (Eger 2005). Theoretically, increased tissue solubility of lipid-emulsified sevoflurane compared with its inhaled form could potentially increase its potency regarding organ protection. It is possible that injectable lipid-emulsified sevoflurane has increased tissue solubility when compared with inhaled sevoflurane as, in the present study, the amount of sevoflurane (g $hour^{-1}$) consumed was significantly higher in the Sevo-E treatment, whereas the Fe′Sevo was significantly lower in the Sevo-E than in the Sevo-Inh treatment. The fact that Fe′Sevo was significantly lower in the injectable treatment suggests that there was a greater hepatic metabolism of sevoflurane resulting either from its supposed increased tissue solubility or from increased tissue distribution, or both.

There are published studies demonstrating the efficacy and safety of the emulsified halogenated anesthetics in protecting the myocardium, lungs and kidneys from ischemic injury (Zaugg et al. 2003; Zhang et al. 2011). No reports were found describing dose rates for the emulsified formulation that could produce myocardial depression similar to the dose-dependent cardiovascular depression that has been demonstrated with the inhaled formulation of the halogenated anesthetics (Eger 2005). Hemodynamic results in this study, although limited, demonstrated no difference between inhaled and IV 8% v/v lipid-emulsified sevoflurane at the dosage rates used. A previous study found that emulsified 8% isoflurane in 30% Intralipid significantly increased HR and f_R in dogs with no significant changes in sAP (Yang et al. 2006). In this study, HR was not significantly different from baseline or between treatments. Hypotension is known to cause an increased HR in isoflurane-anesthetized dogs mainly due to baroreceptor response (Muzi & Ebert 1995). Arterial pressures were not significantly different from baseline for either treatment, or between treatments in this study. Mild-to-moderate hypotension in dogs under sevoflurane anesthesia would be expected, as observed in the present study (Abed et al. 2014). Some of the dogs in Sevo-E experienced severe hypotension, with MAP < 50 mmHg. Although the values were statistically not different from baseline or between treatments, we considered that histamine release in Sevo-E could have been responsible for the hypotension. The authors accept that the hemodynamic evaluation of dogs in this study was limited, but consider the possibility that an increased tissue solubility with the injectable treatment may have changed the distribution of the lipid-emulsified sevoflurane, resulting in the same level of hemodynamic depression as observed with inhaled sevoflurane.

Although there were no differences in f_R and Pe′CO_2 between the Sevo-E and Sevo-Inh treatments, $PaCO_2$ increased and f_R decreased significantly from baseline in the Sevo-E treatment. Respiratory depression has been described in human patients anesthetized with inhaled sevoflurane (Eger 2005). The respiratory acidosis observed in the Sevo-E treatment could have been produced by the significantly higher amount (g $hour^{-1}$) of sevoflurane depressing the central nervous system. As mentioned earlier, increased lipid solubility may increase tissue concentration of the emulsified halogenated anesthetic, producing further respiratory depression. Also, in Sevo-E, a significant reduction in blood HCO_3^- was observed along with a decrease in base excess. There is no clear explanation for the concurrent metabolic acidosis observed in Sevo-E but it was possibly caused by the lipid vehicle used for sevoflurane emulsification. The IV administration of fat-based parenteral nutrition may potentially produce

metabolic acidosis, as most commonly used fat emulsions will donate between 37 and 61 mEq of H^+ ions L^{-1} (Erny et al. 1975).

In one study it was shown that histamine release due to hypersensitivity occurs with sevoflurane nanoemulsion in dogs (Johnson et al. 2011). Although plasma histamine concentrations were not measured, the facial edema in dogs in Sevo-E is a clinical sign associated with histamine release. In one published study, polysorbate 80 was implicated in hypersensitivity when isoflurane-loaded nanoemulsion was administered to dogs (Krahn et al. 2012). Also, histamine release due to hypersensitivity has been described in dogs receiving other drugs with polysorbate 80 (Cober et al. 2009). The production of lipid-emulsified sevoflurane used 30% Intralipid, which is a non-pyrogenic fat emulsion prepared with soybean oil, egg yolk phospholipids, and glycerin. Any of those components could initiate a hypersensitivity reaction in the studied dogs if the dogs had been exposed to those components previously. A similar complication has been described previously with fluorocarbon-based sevoflurane injectable formulation in dogs (Johnson et al. 2011).

Absence of significant biochemical changes between treatments or from baseline demonstrated that sevoflurane lipid emulsion did not produce acute liver or renal dysfunction. Sevoflurane is metabolized through P450 2E1 enzyme to free fluoride and HFIP in humans and dogs (Bradshaw & Ivanetich 1984; Kharasch et al. 1995). Sevoflurane does not produce strong acids when metabolized, in contrast to isoflurane, which is metabolized to trifluoroacetic acid (Bradshaw & Ivanetich 1984; Kharasch et al. 1995).

There were some limitations to this study. First, this is an initial study which shall be followed by other, more detailed investigations into injectable inhalation anesthetics in dogs. Another important limitation is that sevoflurane plasma or tissue concentrations were not determined. Measurement of plasma concentrations of sevoflurane could clarify the hypothesis that an increased sevoflurane solubility in tissues after IV administration of sevoflurane lipid emulsion might augment hepatic sevoflurane metabolism.

Conclusions

This study demonstrated that general anesthesia could be maintained in dogs with 8% v/v emulsified sevoflurane in 30% Intralipid IV. Hypotension, respiratory acidosis, and a mild metabolic acidosis occurred after administration of emulsified sevoflurane IV at the dose rate used in this study. The amount of sevoflurane necessary to maintain general anesthesia in dogs was not decreased by the use of emulsified sevoflurane in 30% Intralipid when compared with inhaled sevoflurane. Future studies are warranted in order to investigate the clinical use of injectable sevoflurane.

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