Cardiovascular effects of constant rate infusions of lidocaine, lidocaine and dexmedetomidine, and dexmedetomidine in dogs anesthetized at equipotent doses of sevoflurane


Abstract — This study evaluated the cardiovascular effects of a constant rate infusion (CRI) of lidocaine, lidocaine and dexmedetomidine, and dexmedetomidine in dogs anesthetized with sevoflurane at equipotent doses. Treatments consisted of T1-Lidocaine [loading dose 2 mg/kg body weight (BW), IV, and CRI of 100 µg/kg BW per min] at 1.4% end-tidal of sevoflurane (FE_SEV); T2-Dexmedetomidine (loading dose 2 µg/kg BW, IV, and CRI of 2 µg/kg BW per hour) and FE_SEV 1.1%; and T3-Lidocaine-Dexmedetomidine using the same doses of T1 and T2 and FE_SEV 0.8%. Constant rate infusion of lidocaine did not induce any cardiovascular changes; lidocaine and dexmedetomidine resulted in cardiovascular effects similar to dexmedetomidine alone. These effects were characterized by a significant (P < 0.001) decrease in heart rate, cardiac output, cardiac index, oxygen delivery, and pulmonary vascular resistance index, and a significant (P < 0.001) increase in mean and diastolic arterial pressure, systemic vascular resistance index, pulmonary arterial occlusion pressure and oxygen extraction ratio, compared with baseline values. In conclusion, a CRI of lidocaine combined with dexmedetomidine produces significant cardiovascular changes similar to those observed with dexmedetomidine alone.

Résumé — Effets cardiovasculaires des infusions constante de taux de lidocaïne, lidocaïne et dexmétidoméidine, et dexmétidoméidine chez chiens anesthésiés à équipotent doses de sevoflurane. L’objet de cette étude a été la evaluation des effets cardiovasculaires de la perfusion à débit continu (CRI) de lidocaïne, lidocaïne et dexmétidoméidine, et dexmétidoméidine en chiens anesthésiés avec sevoflurane dans équipotentiel dose. Les traitements consistèrent à T1-Lidocaïne [dose de charge de 2 mg/kg, IV, et perfusion à débit continu (CRI) de 100 µg/kg/min] en 1,4 % en fin d’expiration du sevoflurane (FE_SEV); T2-Dexmétidoméidine (dose de charge de 2 µg/kg, IV, et perfusion à débit continu (CRI) de 2 µg/kg/h) et FE_SEV 1,1 % et T3-Lidocaïne-Dexmétidoméidine en utilisant la même dose de T1 et T2 et FE_SEV 0,8 %. Perfusion à débit continu (CRI) de lidocaïne ne induit pas aucun échange cardio-vasculaire; lidocaïne et dexmétidoméidine resulta dans effets cardio-vasculaires similaires a dexmétidoméidine seule. Ces effets caractérées par significative décroissance (P < 0.001) en fréquence cardiaque, le débit cardiaque, index cardiaque, la libération de l’oxygène, pulmonaire indice de résistance vasculaire, et significative accroissement de la moyenne a la pression artérielle diastolique (P < 0.001), indice de résistance vasculaire systémique, et l’extraction d’oxygène. En somme, la perfusion à débit continu (CRI) de lidocaïne produit significative échange cardio-vasculaire similaire à ceux observe en utilisant seulement dexmétidoméidine.

(Traduit par les auteurs)

Can Vet J 2017;58:729–734
Introduction

Maintenance of general anesthesia with inhalational anesthetics allows for adequate control of anesthetic depth and a fast recovery. However, a major concern is the dose-dependent cardiopulmonary depression that occurs with higher concentrations of inhalational anesthetics. The inclusion of an injectable analgesic and/or sedative and/or anesthetic drug allows a more balanced technique and may result in a sparing effect on the minimum alveolar concentration (MAC) of the inhalational anesthetic with a potential reduction in the dose-dependent adverse effects (1–4).

Alpha 2-adrenergic agonists, such as dexmedetomidine and medetomidine, have been included as part of balanced anesthetic techniques in dogs and other species, due to their analgesic and inhalational anesthetic sparing effects (2,4–11). Their profound effects on the cardiovascular system at doses commonly used in veterinary practice include a decrease in cardiac output, heart rate, sympathetic tone, and an increase in afterload from increases in systemic vascular resistance, which may result in an increase in systemic and occasionally pulmonary pressures (11–18). These effects can be minimized and shortened when low doses are administered in humans and dogs (2,5,7,10,14,18–21).

Lidocaine has been used intravenously as an analgesic during surgery and for its MAC sparing properties with minimal cardiovascular effects in dogs and horses (3,4,22–27). The cardiorespiratory effects of a combination of lidocaine and medetomidine as a constant rate infusion (CRI) for balanced anesthesia have been determined in horses and included higher blood pressure, less isotropic support, lower inhalational anesthetic requirements, and similar cardiac index when compared to a control group (6,28). The MAC sparing effects for isoflurane and sevoflurane of a combination of CRIs of lidocaine and dexmedetomidine have been determined in dogs (29,30), but not the cardiopulmonary effects of these CRIs with sevoflurane. The purpose of this study was to investigate if the benefits observed in other species from CRIs of lidocaine and/or dexmedetomidine combined with inhalational anesthetics are also present in dogs anesthetized with sevoflurane at equipotent doses. Our hypothesis was that in sevoflurane-anesthetized dogs, a CRI of dexmedetomidine with or without lidocaine is characterized by dexmedetomidine cardiovascular effects, compared with a CRI of lidocaine alone.

Materials and methods

Animals

Three male and 3 female adult mixed breed neutered dogs, 3.4 ± 0.8 y old (mean ± SD), weighing 18.4 ± 5 kg were included in a prospective randomized crossover experiment with a 2-week washout period between treatments. Dogs were healthy based on medical history, physical examination, complete blood (cell) count (CBC), and serum biochemical analysis. The Animal Research Ethics Committee of the Universidad Autónoma de Mexico approved this study (protocol # DCARM-1412).

Anesthetic procedure and instrumentation

Food but not water was withheld for 8 h prior to each anesthetic procedure. A 20-gauge catheter (BD; Becton Dickinson and Company, New Jersey, USA) was aseptically placed into the cephalic vein. Anesthesia was induced via facemask using a vaporizer setting of 8% of sevoflurane (Sevorane; Abbott Laboratories, Bogotá, Colombia) and a fresh gas flow of 4 L/min. Dogs were orotracheally intubated and attached to a circle anesthetic rebreathing system (Fabius; Dräger Medical GmbH 23542, Lübeck, Germany), placed in lateral recumbency and mechanically ventilated with intermittent positive-pressure ventilation (IPPV) to maintain eucapnia (35 to 40 mmHg end tidal CO₂). Monitoring included end-tidal sevoflurane and CO₂ concentrations using a side-stream infrared gas analyzer (Dräger Vamos; Dräger Medical GmbH) with the sampling port attached between the endotracheal tube and the breathing system. The anesthesia monitor was calibrated each morning using a calibration gas specifically designed for this purpose (DOT-34 NRC 300/375M1014; Datex-Ohmeda Division, Helsinki, Finland). Anesthesia was maintained with sevoflurane vaporized in 100% oxygen with a flow rate of 2 L/min and the end-tidal concentration (FE₃₅₀) maintained at 2.8% while the instrumentation was completed.

An isotonic fluid solution (Hartman Solution, HT, Pisa Agropecuaria, Mexico) was administered at a flow rate of 3 ml/kg body weight (BW) per hour through the cephalic catheter by use of an infusion pump (Colleague; Baxter Healthcare Corporation, Deerfield, Illinois, USA). An electrocardiogram (lead II) for heart rate (HR) and rhythm was continuously monitored by placing electrodes at the level of the elbows and left patella, and a pulse oximeter probe attached to the dog’s tongue (BeneView T8; Shenzhen Mindray Bio-Medical Electronics, Shenzhen, China). A 22-gauge catheter was aseptically placed in the dorsal metatarsal artery and attached to a transducer (DTX plus DT 4812; Becton Dickinson Critical Care Systems, Singapore). The transducer was previously verified against a mercury manometer at 50, 100, and 200 mmHg, and zeroed at the level of the manubrium for direct monitoring of arterial blood pressure [systolic (SAP), diastolic (DAP), and mean (MAP)]. Blood was collected and placed into lithium heparin syringes (A-Line; Becton, Dickson and Company, Oxford, UK), for determination of pH, arterial partial pressure of carbon dioxide (PaCO₂) and oxygen (PaO₂), packed cell volume, hemoglobin, bicarbonate, lactate, and glucose at the dog’s corrected body temperature, using a blood gas analyzer (GEM Premier 3000; Instrumentation Laboratory, Warrington, UK). The gas analyzer was calibrated before each experiment by using 2 aqueous buffered solutions containing precise concentrations of CO₂ and O₂.

A 7-Fr 4 lumen 110 cm Swan-Ganz catheter (Arrow Balloon Thrombolysis Set; Arrow International, Morrisville, North Carolina, USA) was introduced through the jugular vein using an introducer (Introducer kit; Arrow International) for determination of cardiac output (CO) by thermodilution (COM-1 Cardiac Output Computer; Edwards Life Sciences, Irvine, California, USA). The distal port of this catheter was connected to another pressure transducer and advanced into the pulmonary artery using the characteristic pressure wave changes associated with the right ventricle and pulmonary artery. The transducer was connected to the distal port of the Swan-Ganz catheter,
zeroed at the level of the manubrium to allow measurement of mean pulmonary arterial pressure (MPAP) and pulmonary arterial occlusion pressure (PAOP), and switched to the proximal port for measurement of central venous pressure (CVP). For CO determinations, 5 mL of dextrose (Dextrose 5%; Solution DX-5; Pisa Farmaceutica, Mexico City, Mexico) iced to a temperature of 1°C to 4°C was rapidly hand-injected into the proximal port of the Swan-Ganz catheter at end-expiration. At each measurement time, 3 consecutive measurements that were within 10% of each other were recorded and their average taken as CO (L/min).

The thermistor on the Swan-Ganz catheter was used to measure core body temperature (T), which was maintained between 37.5°C and 38°C. Samples of mixed venous blood were anaerobically collected for gas analysis.

**Experimental protocol and measurements**

The FE\textsubscript{SEV} was adjusted to 1.8% after instrumentation and maintained for 30 min to establish baseline values for CO, HR, CVP, SAP, DAP, MAP, and MPAP. From these values, the following parameters were calculated:

- cardiac index (CI) (mL/min per kg BW), CI = CO/BW;
- stroke volume index (SVI; mL/beat per kg BW), SVI = CI/HR;
- pulmonary vascular resistance index (PVRI; mmHg/mL per min per kg BW) = [(MPAP — PAOP)/CI];
- systemic vascular resistance index (SVRI; mmHg/mL per min per kg BW) = [(CVP — MAP)/CI];
- oxygen delivery (DO\textsubscript{2}; mL O\textsubscript{2}/min per kg BW) = \((\text{Hemoglobin} \times \text{Saturation} \times 1.34) + (0.0031 \times \text{PAO}_2);\)
- oxygen consumption (VO\textsubscript{2}; mL O\textsubscript{2}/min/kg BW) = \((\text{CaO}_2 — \text{Cmvo}_2 \times \text{Cl})/100, \), where \(\text{Cmvo}_2\) (mixed venous oxygen content in mL O\textsubscript{2}/dL) = (Hemoglobin \times Saturation \times 1.34) + (0.0031 \times \text{Pvo}_2);\) and
- oxygen extraction ratio (ERO\textsubscript{2}; %) = (VO\textsubscript{2}/DO\textsubscript{2}) \times 100 (31).

Each dog received 1 of the following 3 treatments on separate anesthetic occasions, assigned by a randomization scheme (http://www.randomization.com), T1-Lidocaine (LID)-loading dose of lidocaine (LidoSina 2% Inyectable: Pisa, México), 2 mg/kg BW, IV, followed immediately by a CRI of 100 μg/kg BW per min; T2-Dexmedetomidine (DEX)-loading dose of dexmedetomidine (Dexdomitor; Orion Corporation, Espoo, Finland), 2 μg/kg BW, IV, followed by a CRI of 2 μg/kg BW per hour; and T3-Lidocaine-Dexmedetomidine (LID-DEX) at the same doses as T1 and T2. Loading doses were diluted up to a final volume of 3 mL with sterile water and injected over 10 s. Treatments for the CRI were diluted into 60 mL of saline (Saline 0.9%; Solution DX-CS; Pisa Farmaceutica) and delivered using a pump infusion device (Colleague; Baxter Healthcare Corporation). The solution for the LID group was prepared by adding 6 mL of lidocaine 2% to 54 mL of saline, resulting in 2 mg of lidocaine per mL. For the DEX group, 0.08 mL of dexmedetomidine 0.05% was added to 59.9 mL of saline, resulting in 0.66 μg of dexmedetomidine per mL. For the LID-DEX group, 6 mL of lidocaine and 0.08 mL of dexmedetomidine were added to 53.9 mL of saline, resulting in the same concentrations of each drug as for the LID and DEX groups. These concentrations correspond to an infusion rate of 0.05 mL/kg BW per min of any of the solutions. The FE\textsubscript{SEV} was decreased for each treatment to 1.4% for group LID, 1.1% for group DEX, and 0.8% for group LID-DEX, based on MAC equipotent doses previously determined (30). A second set of measurements was completed after 45 min of CRI administration.

For recovery from anesthesia the CRIs and sevoflurane administration were discontinued. Upon return of reflexes and spontaneous breathing, the dogs were disconnected from the anesthesia machine and extubated when a swallowing reflex was present. After recovery, dogs received carprofen (Rimadyl); Pfizer Animal Health, Capelle a/d I Jssel, The Netherlands) 4 mg/kg BW, SQ, q24h for 2 d. All dogs were rehomed after this experiment was completed.

**Statistical analysis**

Statistical analysis was performed using Prism 6.0 computer software (GraphPad Software; La Jolla, California, USA). The Shapiro-Wilk test was used for the assessment of normality. Data were examined with a 2-way repeated measures analysis of variance (ANOVA) to compare the effect of treatment with baseline and for comparisons between treatments. The Holm-Sidak test was used for multiple comparisons between means of treatments (32). Data are reported as mean ± standard deviation (SD). Statistical significance was accepted at \(P < 0.05\).

**Results**

Baseline values for each of the 3 treatments were completed approximately 45 min after induction (Table 1). Following the dexmedetomidine CRI administration, HR, CO, CI, PVRI, and DO\textsubscript{2} were significantly decreased with respect to baseline in both the DEX and LID-DEX groups (\(P < 0.0001\)) and the LID CRI group; whereas MAP (\(P < 0.0005\)), PAOP (\(P < 0.0001\)), SVRI (\(P < 0.0001\)), and O\textsubscript{2}ER (\(P < 0.0001\)) were significantly increased in both the DEX and LID-DEX groups with respect to baseline and the LID group. All dogs receiving dexmedetomidine (DEX) showed second-degree atrioventricular block in the first 20 min after administration.

Arterial blood gas values, lactate, and glucose were within normal range and not significantly different between groups. Mean and SD lower and upper values were 7.38 \(±\) 0.009 for pH, 35 \(±\) 1.0 and 37 \(±\) 1.2 mmHg for PaCO\textsubscript{2}, 487 \(±\) 25 and 503 \(±\) 16 mmHg for PaO\textsubscript{2}, 22 \(±\) 1 and 23 \(±\) 2 mmol/L for bicarbonate, 1.0 \(±\) 0.1 and 1.1 \(±\) 0.1 mmol/L for lactate, and 9.1 \(±\) 2.0 and 9.8 \(±\) 1.1 mmol/L for glucose.

**Discussion**

In this study equipotent anesthetic doses of LID-DEX and DEX in combination with sevoflurane in dogs resulted in similar cardiovascular effects, characterized by significant increases in SVR and MAP, with concomitant decreases in HR and CO, compared with an equipotent dose of LID combined with sevoflurane, which did not induce any alterations in cardiovascular parameters. The cardiovascular effects in the
LID-DEX and DEX groups are mostly related to the effects of DEX, which are induced in both conscious and anesthetized dogs (2,5,7,9–12,17,20). Similar cardiovascular effects of increased MAP and decreased HR and CO have been reported in horses anesthetized with isoflurane, receiving CRIs of LID-medetomidine when compared to LID (6). In our study the decrease in CO from baseline in the DEX group (42%) and LID-DEX group (41%) was due to a decrease in HR that was of similar magnitude within each group, since CO = HR × SV, and SV was not affected by either treatment. Cardiac output was not affected in the LID group, similar to another study in healthy dogs and dogs with subaortic stenosis administered doses of up to 200 μg/kg BW per min (33).

The effects of medetomidine and DEX on CO are dose-related (7,10,11,17,21). In isoflurane-anesthetized dogs, medetomidine, which is considered half as potent as DEX for its sedative and cardiorespiratory effects (34,35), caused a decrease in CO of 15%, 22%, 27%, 44%, 48%, and 61% with IV loading doses of 0.2, 0.5, 1.0, 1.7, 4, and 12 μg/kg BW, followed by equal corresponding CRIs (μg/kg BW per hour), respectively (7). Similarly, in isoflurane-anesthetized dogs, DEX caused a decrease in CO of 19%, 30%, and 58% with IV loading doses of 0.5, 1.2, and 3 μg/kg BW, followed by equal corresponding CRIs (μg/kg BW per hour), respectively (10,17). In our study, the approximately 40% decrease in CO from administering an IV dose of 2 μg/kg BW and CRI of 2 μg/kg BW per hour of DEX in sevoflurane-anesthetized dogs is also in agreement with those studies.

Heart rate is also affected in a dose-dependent manner by medetomidine and DEX in isoflurane-anesthetized dogs. In general, lower loading doses followed by equal corresponding CRIs (μg/kg BW per hour) of medetomidine (< 1.7 μg/kg BW) decreased HR to a maximum 36%, whereas higher doses (> 4 μg/kg BW) and equal corresponding CRIs (μg/kg BW per hour) decreased HR by up to 45% (7). For DEX, lower doses (< 1.2 μg/kg BW) followed by equal corresponding CRIs (μg/kg BW per hour) decreased HR to a maximum of 33%, whereas doses of 3 μg/kg BW and equal corresponding CRIs (μg/kg BW per hour) decreased HR by up to 62% (2,10,17).

In our study, HR decreased by 39% in the DEX group, using a dose of 2 μg/kg BW and CRI of 2 μg/kg BW per hour. This dose is equivalent to 4 μg/kg BW per hour of medetomidine and the decrease in HR is similar to the 45% decrease induced by that dose (7). The decrease in HR in the DEX-LID was less (33%), and although not significantly different from the DEX group, it could have been less because LID has a vagolytic effect under conditions of increased vagal activity, which results in an increase in the rate of discharge between the sinoatrial node and upper Bundle of His (36). Baseline HR did not change after administration of LID in the LID group, which is similar to results from other studies in dogs anesthetized with isoflurane or sevoflurane (3,4,25,29,30), and has also been shown to increase with LID (33).

Pulmonary arterial occlusion pressure increased from baseline by 118% and 92% in the DEX and LID-DEX groups, respectively. The SVRI followed a similar pattern, increasing by 119% and 125%, respectively. Similar findings are reported in other studies for these 2 variables in dogs and cats (10,17,37). The increase in PAOP is the result of a lower CO (38), whereas the increase in SVRI is through direct vasoconstriction actions of alpha-2 agonists on the smooth muscle of blood vessels (39). In our study MPAP did not change, which is similar to other studies in halothane-anesthetized dogs and halothane-anesthetized sheep that received medetomidine (11,40), but PVRI decreased significantly in our study in the DEX and LID-DEX group, due to the increase in PAOP. Other studies have also shown no significant changes in PVRI after medetomidine (40). Differences between vascular resistance of the pulmonary and systemic circulation have been attributed to the alpha-receptor density, which is lower in the pulmonary than the systemic vasculature and may partly
explain the attenuated vasoconstrictor response of the pulmonary circulation (41). Despite the observed cardiovascular effects of alpha-2 agonists, their use has become more popular in healthy patients undergoing surgery due to their potent analgesic and sedative effects. However, the cardiovascular effects of alpha-2 agonists have not been thoroughly evaluated in dogs undergoing surgical stimulation, so it is not known if the changes and their magnitude, as determined in this and other studies, are consistent in patients in whom sympathetic activity from nociceptive input is more likely to occur. One study demonstrated MAP to be stable and within acceptable limits (99 mmHg) with HR of 49 to 68 beats/min in dogs undergoing soft tissue or orthopedic surgery under isoflurane anesthesia, while receiving a CRI of 1, 2, or 3 μg/kg BW per hour of DEX after IV pre-medication with 5 μg/kg BW (5). In another study in dogs undergoing ovariohysterectomy, medetomidine (1 μg/kg BW and a CRI of 1 μg/kg BW per hour) was administered after induction and before the start of surgery and decreased HR immediately after, but increased steadily to baseline throughout surgery, whereas CI did not change from baseline and during surgical stimulation, and SAP remained stable from baseline and only increased significantly during removal of the ovaries (9). A decrease in CO has a direct effect on oxygen delivery (DO2), since the latter is the product of the CO and CaO2. Consequently, O2 ER is also affected since it is the ratio of VO2 and DO2. Decreases in DO2 and increases in O2 ER were shown in this and other studies when dexmedetomidine is used (10,17); however, if blood lactate concentrations remain unchanged despite a decrease in DO2 and an increase in O2 ER, it should indicate that tissues can maintain aerobic metabolism, reflecting that CO is still adequate under these conditions. We did not detect changes in lactate concentrations, despite a decrease in DO2 and an increase in O2 ER. Similarly, lactate levels remained unchanged in dogs undergoing surgery while receiving a CRI of DEX or medetomidine (5,9). Despite affecting CO, the reduction in blood flow caused by DEX has been shown in dogs to preferentially affect the skin and spleen, whereas blood flow to heart, brain, liver, intestine, and kidneys remains well preserved and above levels that induce underperfusion, which was also supported by unchanged lactate concentrations (14).

In conclusion, the administration of DEX or the combination of Lid-DEX produces significant hemodynamic changes resulting in decreased CO, HR, and increased SVR pressure and PAOP in dogs anesthetized with sevoflurane; however, such changes were not associated with compromised tissue perfusion in research healthy dogs.

Acknowledgment

This work was funded by the Mexican National Center for Science and Technology (CONACYT).

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