Hemodynamic Effects of an Intravenous Infusion of Medetomidine at Six Different Dose Regimens in Isoflurane-Anesthetized Dogs*,†

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CLINICAL RELEVANCE

This study investigated the dose dependency of the hemodynamic effects of IV medetomidine (MED) constant-rate infusion (CRI) during isoflurane anesthesia. Twenty-four healthy beagles randomly received one of six MED CRI regimens. A loading dose of MED was administered IV at 0.2, 0.5, 1.0, 1.7, 4.0, or 12.0 $\mu g \cdot kg^{-1}$ for 10 minutes, followed by a maintenance CRI providing identical dose amounts over 60 minutes. Heart rate and mean arterial blood pressure were recorded, blood gases were analyzed, and cardiac index (CI) was determined. Statistical analysis involved a repeated measures linear model. Baseline CI demonstrated a dose-dependent decrease as the MED dose increased, with decreases of 14.9% (SD, 12.7%), 21.7% (17.9%), 27.1% (13.2%), 44.2% (9.7%), 47.9% (8.1%), and 61.2% (14.1%) at doses of 0.2, 0.5, 1.0, 1.7, 4.0, and 12.0 $\mu g \cdot kg^{-1}$, respectively. The four lowest doses induced limited and transient changes in heart rate, mean arterial pressure, and CI. Further investigation into potential perioperative uses of MED CRI is warranted.

INTRODUCTION

Medetomidine (MED) is a highly potent and selective α_2-agonist that has sedative, anxiolytic, muscle relaxant, and analgesic properties. When used perioperatively, it reduces the need for other anesthetic agents, and it is used widely for sedation and premedication before general anesthesia in small animals.[1] MED is supplied in a 50:50 racemic mixture of two optical enantiomers (dexmedetomidine [DMED] and levomedetomidine [LMED]), of which DMED is the active enantiomer.[2,3] MED has a very high affinity for α_2-adrenoceptors, acting as a full agonist, and possesses a selectivity ratio of 1620:1 (α_2:α_1), which is five to 10 times higher than that of xylazine (α_2:α_1 ratio, 160:1) or detomidine (α_2:α_1 ratio, 260:1).[2]

MED is licensed in North America to be administered IM or IV. After IM administration, absorption of the drug is rapid: peak serum levels are reached within 30 minutes.[4] When the drug is given IV, the onset of action is rapid and the peripheral cardiovascular effects are more pronounced than with IM administration.[5] Because of MED's significant sedative, analgesic, and anesthetic-sparing effects, low doses are adequate for perioperative use when given with other anesthetic/analgesic drugs.[6]

Despite its analgesic and perioperative stress response–reducing effects,[7] MED has not been used to its full potential in veterinary medicine. Unfortunately, α_2-adrenoceptor agonist administration, particularly IV, is associated with major adverse effects on the cardiovascular system. These effects include a biphasic blood pressure response (hypertension followed by normo- or hypotension) with reflex bradycardia and decreased cardiac output (CO) and/or cardiac index (CI), increased systemic vascular resistance (SVR) index and central venous pressure (CVP), and bradydysrhythmias.[8,9] These hemodynamic effects have popularized the use of low-rate MED or DMED IV infusions in an attempt to improve the risk:benefit ratio. Although several reports in the literature describe the clinical potential of this administration strategy,[10–13] to our knowledge, no previous study has quantified the dose dependency of

the hemodynamic effects of MED constant-rate infusion (CRI) to determine a dose rate that optimizes cardiovascular safety.

It has been reported that the cardiovascular effects of MED after IV bolus administration in conscious dogs do not follow a clear dose–response relationship based on evaluation of time–effect data.[5] It is possible that failure to reveal such a dose–response relationship is related to individual variation in the drug's disposition pharmacokinetics. The aim of this study was to quantify the dose dependency of the cardiovascular and hemodynamic effects of MED administered as a CRI in isoflurane (ISO)-anesthetized dogs. Despite the recent quantification of the minimum alveolar concentration–sparing effect of DMED CRI,[11] the dose–response effects of MED or DMED on the degree of cardiovascular depression have yet to be determined as far as we know, and this information is necessary to establish an optimal dose rate. Two studies[12,13] investigating DMED CRIs in dogs were published recently. In one, a clinical study, three doses (1, 2, and 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of DMED given to dogs undergoing ISO anesthesia resulted in acceptable mean arterial blood pressure (MAP) and adequate tissue perfusion.[13] A second, experimental study using a single dose (25 $\mu g \cdot m^{-2} \cdot h^{-1}$) of DMED CRI compared cardiovascular and respiratory effects between dogs undergoing propofol or ISO anesthesia.[12] The investigators reported adequate oxygen delivery and a significant effect of general anesthesia on heart rate (HR), vasoconstriction, and CI. To test the hypothesis that the intensity and duration of the hemodynamic changes associated with MED exposure vary as a function of dose rate, we administered MED at six different CRI dose rates. Furthermore, identification of a CRI dose rate that has minimal hemodynamic effects but maintains what previously has been proposed as an analgesic plasma concentration of MED[14] would be of great interest.

Despite its analgesic and perioperative stress response–reducing effects, MED has not been used to its full potential in veterinary medicine.

MATERIALS AND METHODS

Animals

Clinically healthy, purpose-bred laboratory beagles (n = 24; 13 spayed females and 11 castrated males) were used in this study. The dogs were 1 to 3.5 years of age and weighed between 8.6 and 16 kg. They were housed in groups of six or seven in large pens. Commercial dog food was given once daily, and water was freely available. The care and use of the dogs complied with Canadian Council for Animal Care guidelines,[15] and the animal care committee of the Faculty of Veterinary Medicine of the Université de Montréal approved the study protocol (05-Rech-1298). All procedures were performed during the day, with two experiments completed during each study day. The night before each study day, the dogs were brought to single cages, where water was given and food was withheld. They were fed following full recovery from the experiment. All dogs were accustomed to handling and instrumentation.

Treatments

Each dog randomly received one of six treatments (six groups, n = 4 per group) in a prospective, controlled, blinded design. MED

hydrochloride (Domitor; Orion Pharma, Espoo, Finland/Pfizer Animal Health, Kirkland, QC, Canada) was administered IV over 10 minutes at a manual loading infusion rate of 1.2, 3.0, 6.0, 10.2, 24.0, or 72.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, followed by a 60-minute maintenance CRI at automated rates of 0.2, 0.5, 1.0, 1.7, 4.0, and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively. ISO (AErrane; Baxter Corp., Mississauga, ON, Canada) was administered during the entire experiment, including the time required for instrumentation and stabilization, a resting time during which baseline values were recorded before MED administration, the 70-minute–long exposure to MED combined with ISO, and a 60-minute follow-up (ISO alone) after the MED CRI.

Study Procedure

Each treatment was initiated by mask induction with ISO in oxygen. The dogs were intubated, and general anesthesia was continued with the use of a Bain nonrebreathing system (Moduflex Coaxial; Dispomed, Joliette, QC, Canada) by maintaining the end-tidal ISO concentration (ET-ISO) at a constant level of approximately 1.0 minimum alveolar concentration (i.e., 1.3% to 1.4% in dogs[16]) and the end-tidal CO_2 at 35 to 45 mm Hg with controlled intermittent positive-pressure ventilation (Hallowell EMC Model 2000 ventilator; Hallowell Engineering & Manufacturing Corp., Pittsfield, MA). During the experiment, body temperature was monitored and stabilized at 37.0°C with warm water–circulating heating mats (Micro-Temp II 747; Cincinnati Sub-Zero Products, Inc., Cincinnati, OH). After initiation of intermittent positive-pressure ventilation, a 22–standard wire gauge (SWG) cannula (BD Insyte-W catheter; BD Infusion Therapy Systems, Sandy, UT) was placed in the dorsal pedal artery of a pelvic limb to directly monitor the systemic blood pressure and CO and to collect arterial blood samples. Two 20-SWG cannulas (BD Angiocath IV catheter; BD Infusion Therapy Systems) were placed in each cephalic vein: one for MED infusion and the other to allow IV administration of fluid (0.9% sodium chloride Injection, USP; Baxter Corp.) at a rate of 10 $mL \cdot kg^{-1} \cdot h^{-1}$ and lithium chloride (LiCl injection; LiDCO Ltd., London, UK). A 20-SWG cannula was placed in a jugular vein for venous blood sampling. The dogs were placed in lateral recumbency, and the arterial cannulas were connected to a transducer (pressure monitoring kit with TruWave Disposable Pressure Transducer; Edwards Lifesciences, Irvine, CA) connected to a multiparametric vital signs monitor (Life Window LW-6000; Digicare Biomedical Technology, Boynton Beach, FL). The pressure transducer was adjusted to heart level. At 5-minute intervals from baseline until the end of the 130-minute anesthesia period, the vital signs monitor recorded HR; lead II electrocardiography; direct systolic arterial pressure, diastolic arterial pressure, and MAP; pulse oximetry; capnography; ET-ISO; and rectal temperature. Systemic blood pressures and HR were allowed to stabilize (three consecutive measurements with minimal variation: HR ± 5 bpm, MAP = 60 ± 15 mm Hg) before baseline values were recorded. Respiratory rate and tidal volume were also monitored and stabilized during the study.

The lithium dilution method (LiDCO Ltd.) was used to measure CO and calculate CI, once at baseline and then every 10 minutes during the 130-minute anesthesia period. The CO and CI values were determined by use of a commercial computer (LiDCO plus hemodynamic monitor HM 71-02, LiDCO Ltd.); measurements were performed according to the manufacturer's instructions and reports of use in small animals.[17,18] Lithium chloride (5 $\mu mol \cdot kg^{-1}$) was administered for each CO measurement through the cannulated cephalic

vein.[17] The SVR was calculated with the formula SVR = (80 × [MAP – CVP])/CO; an average value of 4 mm Hg was used for CVP.

The MED loading doses were diluted with isotonic saline to a final 2-mL volume. Doses were hand-injected IV via 3-mL syringes over 10 minutes. All maintenance infusion doses were diluted with isotonic saline to a final 30-mL volume and were administered through a cephalic venous cannula with an infusion pump (Harvard Apparatus 22, Model 55-2222; Harvard Apparatus, Holliston, MA) over 60 minutes. Calibrated infuser pumps were used, and the program settings were double-checked before each use.

Arterial and venous blood samples were taken from the pedal artery and jugular vein cannulas via syringes connected to three-way stopcocks. The first 1 mL of blood diluted with the heparinized saline lock was discarded, the sample collected, and the cannula flushed with isotonic heparinized saline solution. Arterial and venous samples were drawn simultaneously via 1-mL heparinized (Hepalean, heparin sodium injection USP 10,000 IU·mL^{-1}; Organon, Toronto, ON, Canada) syringes for blood gas analysis at baseline (for control values) and at 15 and 45 minutes after starting the loading dose, placed on ice immediately after sampling, and analyzed within 15 to 30 minutes (Stat Profile M; Nova Biomedical, Waltham, MA). Blood gas values were corrected to body temperature. In addition to arterial and venous pH, oxygen and carbon dioxide tensions, plasma glucose, lactate, and HCO_3^- concentrations were analyzed. Venous blood samples (5 mL) were collected into 10-mL dry vacuum tubes for drug concentration analysis before the beginning of the MED loading dose and at 5, 15, and 45 minutes after the start of the CRI. Additional venous samples were drawn at 30 and 60 minutes after the end of the maintenance CRI. Samples were allowed to clot at room temperature for 30 to 60 minutes and were centrifuged for 15 minutes at 1000 ×*g* at room temperature; serum was harvested and stored at –80°C pending analysis with liquid chromatography–electrospray ionization tandem mass spectrometry techniques (LC-MS/MS system PESciex API 3+; Applied Biosystem/MDS Sciex, Concord, ON, Canada). The calibration curve was linear over the whole analytical range, with a lower limit of quantification of 0.05 µg/L; precision coefficient of variation was ≤11.1%, and bias was ≤6%. Quality control samples provided by Fermion (a division of Orion Pharma) were analyzed on blind conditions with satisfactory results.

Statistical Analyses

All numerical variables were analyzed using repeated-measures linear mixed-effect models. All models were built with dose, time, and the time × dose interaction as fixed-effect variables, and the animal was nested into treatment as a random-effect variable. The variance–covariance matrix of the data was modeled according to a strategy described by Littell et al.[19] Briefly, a mixed-effect model containing no interaction was estimated with a free covariance structure. The model was then reestimated with more parsimonious covariance matrices (*e.g.*, variance components, compound symmetry, and first-order autoregressive), the structures of which resembled that of the unstructured covariance matrix. The final covariance model was selected according to the value of the Schwarz Bayesian criterion.[19] Several a priori contrasts were performed to explore differences between pairs of means: (a) differences between mean values at each time during the MED phase and the overall pretreatment mean for each treatment, and (b) a comparison between mean values of each treatment at each time period. The critical level of significance for all comparisons was $\alpha = 0.05$.

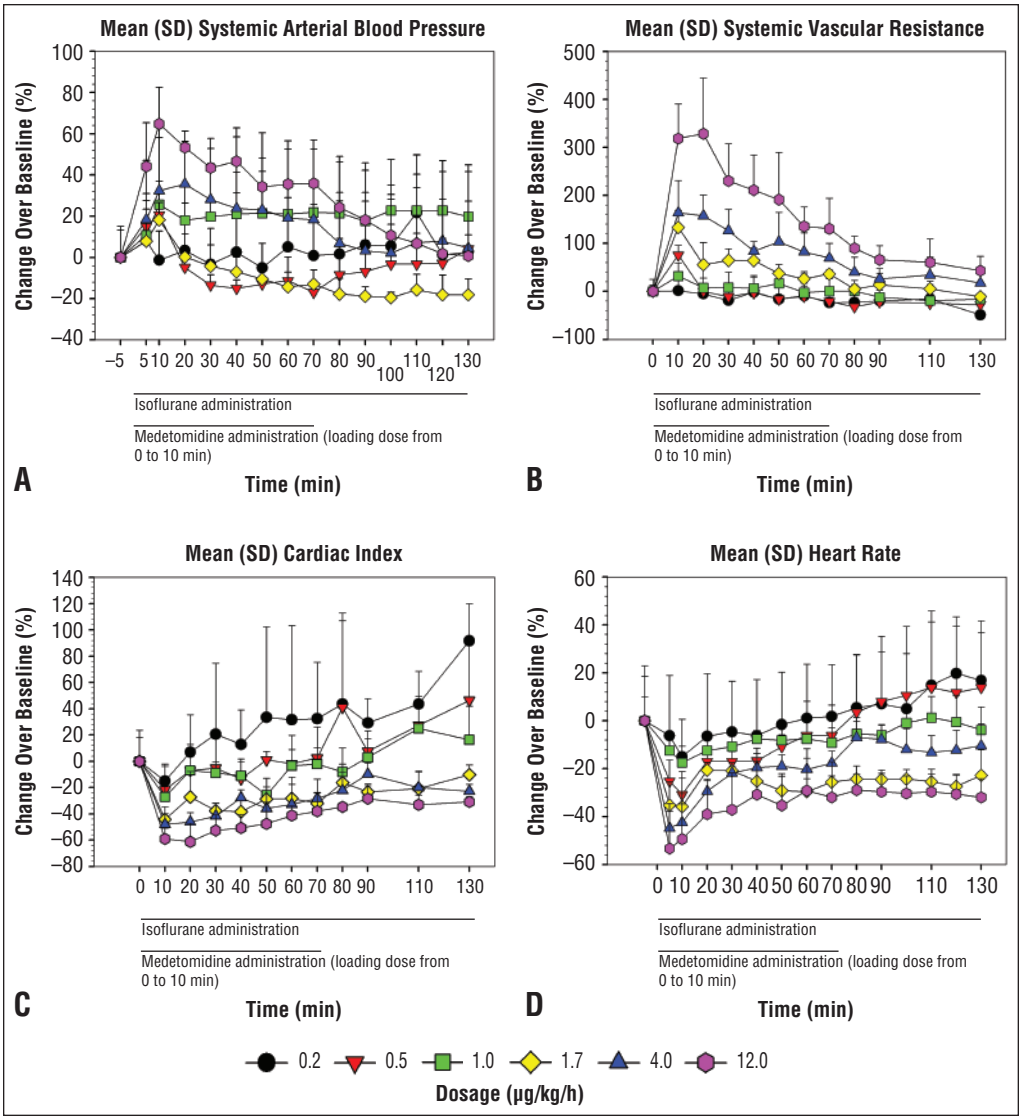

Figure 1. *Changes in mean systemic arterial blood pressure* (A), *systemic vascular resistance* (B), *cardiac index* (C), *and heart rate* (D) *during administration of isoflurane and six doses of medetomidine (MED) constant-rate infusion (CRI), shown as the percentage change (SD) from each dosage group's mean baseline values. MED loading dose administration began at 0 minutes; MED CRI began at 10 minutes and was completed at 70 minutes.*

RESULTS

There was an even distribution of gender (two males and two females per group) for all doses except the 1.7-µg·kg^{-1}·h^{-1} dose, for which there were three females and one male. Body weight did not significantly differ across dos-

TABLE 1. Hemodynamic Parameters Measured at Baseline (–5 Minutes), and Characteristics of the Effects of Medetomidine Constant-Rate Infusion During Isoflurane Anesthesia

Parameter	*Dose* ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	*Mean Baseline Value at –5 Minutes (SD)*	*Duration of Statistically Significant Effect (min)*	*Plateau Effect Value*	
				Mean Zenith (SD)	*Mean Nadir (SD)*
MAP (mm Hg)	0.2	59 (8)	Not present	Not present[a]	
	0.5	62 (7)	10	70 (10)[a]	
	1.0	59 (2)	10	74 (23)[b]	
	1.7	73 (20)	10	85 (6)[a]	
	4.0	69 (14)	70	94 (14)[a]	
	12.0	70 (10)	85	116 (12)[a,b]	
SVR	0.2	4782 (1203)	Not present	Not present[a,b,c]	
(dynes·sec·cm^{-5})	0.5	5222 (1407)	10	9178 (1031)[a,d]	
	1.0	4062 (1246)	10	5357 (890)[d,e,f]	
	1.7	3797 (336)	20	8867 (1344)[b,e]	
	4.0	3486 (295)	70	9190 (2365)[c,f]	
	12.0	3780 (493)	130	16,197 (4396)[a,b,c,e,f]	
CI ($L \cdot min^{-1} \cdot m^{-2}$)	0.2	2.3 (0.4)[a,b]	Not present		Not present[a]
	0.5	2.2 (0.5)[c,d,e]	Not present		Not present[b]
	1.0	2.4 (0.4)	Not present		Not present[c]
	1.7	3.3 (0.7)[a,c]	70		1.9 (0.3)
	4.0	3.3 (0.7)[b,d]	80		1.7 (0.3)
	12.0	3.1 (0.7)[e]	130		1.2 (0.4)[a,b,c]
HR ($beats \cdot min^{-1}$)	0.2	96 (22)	05		82 (15)[a,b,c]
	0.5	85 (9)[a]	40		59 (8)[a,d]
	1.0	93 (7)	60		77 (6)[d,e,f]
	1.7	115 (26)	130		74 (14)
	4.0	96 (13)	70		55 (11)[b,e]
	12.0	109 (20)[a]	130		55 (16)[c,f]

[a,b,c,d,e,f] Within a column, values of a given hemodynamic parameter with the same superscript letter differ significantly ($P < .05$). *CI* = cardiac index; *HR* = heart rate; *MAP* = mean systemic arterial blood pressure; *SVR* = systemic vascular resistance (see text for calculation).

ing groups. Data are expressed as mean (SD) unless indicated otherwise.

Hemodynamic Effects

During MED administration, MAP and SVR initially increased and CI and HR initially decreased in a dose-dependent manner (Figure 1 and Table 1). From mean baseline values, MAP transiently increased for durations positively related to dose (Figure 1). The maximal increase was 8.1% (22.9%; not statistically significant), 20.6% (16.5%), 25.7% (39.3%), 18.2% (8.3%), 35.6% (20.5%), and 64.8% (17.7%) for doses of 0.2, 0.5, 1.0, 1.7, 4.0, and

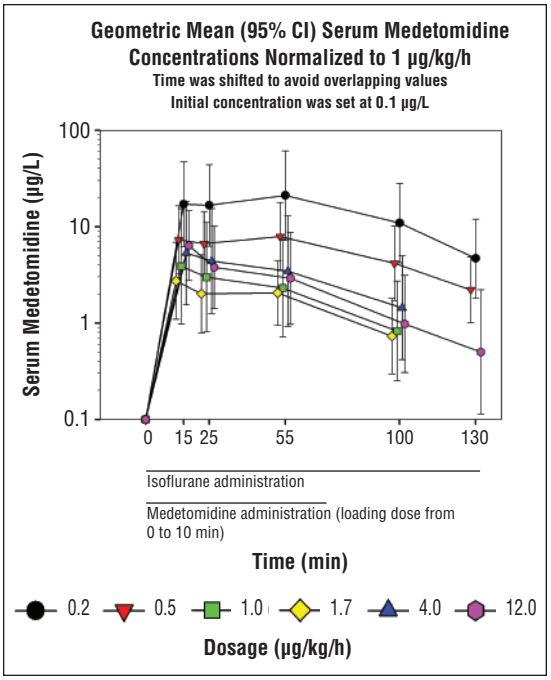

Figure 2. *Mean serum medetomidine (MED) concentrations (with 95% CIs) for the six dosage groups, normalized to 1.0 µg·kg^{-1}·h^{-1} infusion rate. Time was shifted to avoid overlapping values. The initial concentration was set at 0.1 µg/L. Blood samples were obtained at 15, 25, 55, 100, and 140 minutes. MED loading dose administration began at 0 minutes; MED CRI began at 10 minutes and was completed at 70 minutes. A semi-logarithmic scale was used to present data, and artifactually all concentrations started from zero as the baseline value.*

12.0 µg·kg^{-1}, respectively. The effect on SVR was undetected for the 0.2-µg·kg^{-1}·h^{-1} dose and significant only at 10 minutes for the 0.5- and 1.0-µg·kg^{-1}·h^{-1} doses (Figure 1B and Table 1). The maximum increase in SVR was 1.5% (23.8%), 75.8% (19.7%), 32.0% (27.4%), 133.5% (35.4%), 163.6% (67.8%), and 328.5% (116.3%) with increasing dose. Compared with baseline values recorded before starting MED administration, the maximum decrease in CI as MED dose increased was 14.9% (12.7%), 21.7% (17.9%), 27.1% (13.2%), 44.2% (9.7%), 47.9% (8.1%), and 61.2% (14.1%), respectively. The differences between certain group mean baseline CI values were significant ($P < .0322$, Table 1). More precisely, the effect of the three lowest MED infusion rates on CI was not significantly different from baseline ($P > .11$). A significant decrease in HR was observed at all doses, and the return to baseline appeared in a dose-dependent fashion, except for the HR at the 4.0-µg·kg^{-1}·h^{-1} dose, which returned to baseline before the 1.7-µg·kg^{-1}·h^{-1} dose and 10 minutes after the end of MED CRI (Figure 1D and Table 1). HR maximally decreased by 15.1% (15.7%), 30.8% (9.6%), 17.5% (6.8%), 35.9% (11.9%), 44.8% (10.2%), and 53.3% (15.6%) with increasing dose.

When the different doses were compared, the three lowest-dose regimens showed small and short-lived changes in HR, CI, MAP, and SVR that disappeared before the end of each maintenance CRI. Minimal changes were induced by the 0.2-µg·kg^{-1}·h^{-1} dose. The maximal effect on SVR and HR (10 minutes after MED administration commenced; Table 1) with the 0.5-µg·kg^{-1}·h^{-1} dose was greater than that of the 1.0-µg·kg^{-1}·h^{-1} dose. The 1.7-µg·kg^{-1}·h^{-1} dose resulted in greater effects on hemodynamic variables, in magnitude and duration, compared with the three lowest doses. The exception was for MAP in the 1.0-µg·kg^{-1}·h^{-1} dose group, in which a higher MAP apparently persisted for a longer time than in the 1.7-µg·kg^{-1}·h^{-1} group. Altogether, the two largest doses showed physiologically and statistically greater effects on each cardiovascular parameter, and the duration of these effects was longer compared with that of the three lowest doses (Figure 1 and Table 1).

Medetomidine Serum Concentrations

Statistical comparison of the serum MED

concentrations normalized to the unit dose (1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) revealed significant effects of dose and time ($P < .0001$ in both cases), as well as the time × dose interaction ($P = .0001$). As shown in Figure 2, the dose-normalized concentration curves were higher for the 0.2- and 0.5-$\mu g \cdot kg^{-1} \cdot h^{-1}$ groups than for the four higher-dose groups. Of note, the dose-normalized serum MED concentrations during the maintenance CRI continued to increase in the 0.2- and 0.5-$\mu g \cdot kg^{-1} \cdot h^{-1}$ groups, but slightly decreased in the four higher-dose groups. The dose-normalized concentrations in the 0.2-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group differed significantly from those in all the other groups ($P < .0001$ for all pair-wise comparisons). The 0.5-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group differed significantly from the 1.0-, 1.7-, and 12.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ groups ($P < .0485$). Differences between the four highest-dose groups were not statistically significant ($P > .12$).

Other Effects

The arterial pH of some dogs receiving the two highest MED infusions decreased slightly below the physiologic limit (7.35), a difference that reached statistical significance in the 12.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group (Table 2). The values of the other measured respiratory, metabolic, and tissue perfusion variables (glucose, HCO_3^-, $PaCO_2$, and lactate) stayed within a physiologically acceptable range during MED administration for both arterial and venous samples (data for venous samples not shown). Arterial oxygen tension (PaO_2) was maintained in all dose regimens. However, venous oxygen tension decreased significantly with the three highest doses, with a tendency to be dose dependent (Table 2).

DISCUSSION

The dose dependency of the effects of MED on MAP, SVR, CI, and HR was documented quantitatively. The typical α_2-agonist–related increases in SVR and MAP associated with decreases in HR and CI were observed, and the intensity and duration of these effects depended on the CRI dose rate. Therefore, the results strongly suggest that a sigmoid concentration–response relationship exists. The hemodynamic effects were less intense and of shorter duration with the three lowest doses, were more intense and longer lasting with the middle dose (1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and most pronounced with both higher doses. The 0.2-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group showed minimal effects on the intensity and duration of hemodynamic changes, and the effects of the 0.5- and 1.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ groups were similar. Of note, the intensity of the effects on SVR and HR was greater for the 0.5-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group than for the 1.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group, but the magnitude of CI depression was as expected for each group. Also, the duration of these changes became longer with increasing dose. The maximal effects were seen shortly after loading-dose administration with each dose regimen. These results with MED CRI in ISO-anesthetized dogs are comparable with those induced by a bolus IV administration of

The intensity of the effects on SVR and HR was greater for the 0.5-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group than the 1.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group, but the magnitude of CI depression was as expected for each group.

TABLE 2. Parameters Measured in Arterial and Peripheral Venous Samples Before (–10 Minutes) and During Medetomidine Constant-Rate Infusion With Isoflurane Anesthesia in Dogs

			Medetomidine Constant-Rate Infusion with Isoflurane Anesthesia	
Parameter (normal range)	***Dose (μg·kg^{-1}·h^{-1})***	***Mean Baseline Value at –10 Minutes (SD)***	*Mean Value at 25 Minutes (SD)*	*Mean Value at 55 Minutes (SD)*
pH, arterial	0.2	7.38 (0.04)	7.39 (0.04)[a]	7.37 (0.04)[a]
(7.351–7.463)	0.5	7.44 (0.05)[a,b]	7.44 (0.06)[b,c,d]	7.42 (0.06)[b,c]
	1.0	7.39 (0.02)	7.39 (0.02)[e]	7.39 (0.03)[d]
	1.7	7.37 (0.03)[a]	7.36 (0.03)[b]	7.37 (0.03)[b]
	4.0	7.40 (0.03)	7.37 (0.05)*[,c]	7.38 (0.03)*[,e]
	12.0	7.37 (0.07)[b]	7.33 (0.04)*[,a,d,e]	7.32 (0.04)*[,a,c,d,e]
Pa_{O_2}, arterial	0.2	501.0 (39.8)	502.2 (59.6)	512.3 (42.7)
(mm Hg;	0.5	491.3 (73.2)	514.1 (51.6)	490.4 (39.0)
475–675)	1.0	554.7 (4.7)	546.4 (26.4)	550.5 (13.6)
	1.7	448.8 (220.3)	445.8 (218.9)	535.9 (38.8)
	4.0	519.6 (33.6)	547.4 (22.6)	551.7 (26.5)
	12.0	555.1 (26.0)	538.4 (54.0)	536.0 (56.9)
Pv_{O_2}, peripheral	0.2	155.4 (66.6)	162.2 (94.0)	201.8 (95.3)[a]
jugular vein	0.5	136.0 (51.0)	93.5 (19.7)	130.1 (45.7)
(mm Hg;	1.0	192.5 (94.4)	168.2 (119.5)	157.3 (115.6)
75–300)	1.7	210.6 (139.6)	103.3 (18.2)*	104.7 (42.0)*
	4.0	216.7 (56.7)	87.4 (20.4)*	89.5 (18.7)*
	12.0	198 (110.4)	67.1 (12.5)*	78.2 (9.9)*[,a]
Pa_{CO_2}, arterial	0.2	39.0 (5.1)	40.8 (4.8)	46.4 (3.4)*[,a]
(mm Hg;	0.5	39.7 (5.8)	34.5 (1.1)*[,a]	33.9 (4.2)*[,a,b,c,d]
30.8–42.8)	1.0	38.3 (5.4)	39.0 (6.4)[b]	41.5 (6.0)[c]
	1.7	40.5 (1.8)	45.8 (2.6)*[,a,b,c]	42.8 (3.2)[b,e]
	4.0	35.6 (6.2)[a]	40.7 (4.1)*	42.8 (3.1)*[,d]
	12.0	42.5 (4.2)[a]	45.7 (4.7)[c]	45.7 (6.9)[e]

Table continues on page E11

MED in conscious dogs[5]; however, by comparison, our ISO-anesthetized dogs had lower baseline values for MAP, HR, and CI. As a result, the initial hypertensive effects of MED administration were more evident in ISO-anesthetized dogs, allowing better differentiation of their dose–response relationships. No hypotension was subsequently observed. The maximal increase in SVR recorded for our 4.0-μg·kg^{-1}·h^{-1} and 12.0-μg·kg^{-1}·h^{-1} groups was 163.6% and 328.5%, respectively, which is comparable with values recorded in conscious dogs dosed with 5 and 10 μg·kg^{-1} IV MED.[5] After the administration of 1 μg·kg^{-1} MED, the increase in SVR was approximately 210% in conscious dogs, which was markedly higher

TABLE 2. Parameters Measured in Arterial and Peripheral Venous Samples Before (–10 Minutes) and During Medetomidine Constant-Rate Infusion With Isoflurane Anesthesia in Dogs (cont.)

			Medetomidine Constant-Rate Infusion with Isoflurane Anesthesia	
Parameter (normal range)	***Dose ($\mu g \cdot kg^{-1} \cdot h^{-1}$)***	***Mean Baseline Value at –10 Minutes (SD)***	*Mean Value at 25 Minutes (SD)*	*Mean Value at 55 Minutes (SD)*
Glucose, arterial	0.2	5.95 (1.24)	6.18 (0.56)	5.93 (0.51)
($mmol \cdot L^{-1}$;	0.5	5.73 (0.91)	6.10 (0.71)	5.67 (0.55)
3.9–6.0)	1.0	5.43 (1.17)	5.45 (1.10)	5.38 (0.43)
	1.7	5.43 (1.35)	6.33 (0.55)	6.57 (0.47)*
	4.0	5.88 (0.68)	6.33 (0.54)	5.98 (0.77)
	12.0	5.87 (0.95)	5.53 (1.08)	5.48 (0.60)
Lactate, arterial	0.2	N/A	N/A	N/A
($mmol \cdot L^{-1}$;	0.5	N/A	N/A	N/A
0.6–1.8)	1.0	1.55 (0.62)	1.58 (0.69)	1.33 (0.60)
	1.7	1.33 (0.19)	1.08 (0.25)	1.05 (0.33)
	4.0	1.30 (0.69)	1.20 (0.41)	0.85 (0.42)*
	12.0	1.63 (0.61)	1.47 (0.67)*	1.47 (0.93)*
HCO_3^-, arterial	0.2	25.1 (3.4)	25.6 (4.3)	28.8 (4.5)*
($mmol \cdot L^{-1}$;	0.5	27.0 (2.7)[a]	23.6 (3.4)*	22.2 (0.6)*
18.8–25.6)	1.0	23.2 (2.3)	23.4 (3.1)	25.1 (2.8)
	1.7	23.7 (1.6)	26.0 (3.4)	25.0 (3.7)
	4.0	22.6 (3.1)[a]	23.5 (2.8)	25.4 (3.2)*
	12.0	24.7 (2.3)	24.2 (0.6)	23.7 (1.5)

*Within a row, mean value differs significantly from baseline ($P < .05$).
[a,b,c,d,e]Within a column, values with same superscript letter differ significantly ($P < .05$).
N/A = value not available. The normal ranges of the listed parameters have not been validated and are derived from the authors' experience and expertise with the material used.

than that observed in our 1.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group, a difference that may be attributed to the use of bolus administration in conscious dogs (given IV over 5 seconds[a]) instead of an infusion over 10 minutes. The magnitude of the decreases in HR and CI documented in our 1.7-$\mu g \cdot kg^{-1} \cdot h^{-1}$ group was comparable with previous results reported with 1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ MED, in which HR decreased by 41.7% and CI by 41.2%.[10] Data in this study are also consistent with previously reported results with corresponding doses of DMED.[12,20]

Some studies have suggested that the cardiovascular effects of DMED may depend on the initial status of blood vessel tone.[12] It has also been suggested that the central sympatholytic effects may predominate at small doses, which

[a]Pypendop B, Dr. Med. Vet., Dr. Vet. Sci., DACVA; Associate Professor; Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis. Personal communication, 2009.

preferentially stimulate the α_{2A}-adrenoceptor subtype and produce the characteristic sedation and analgesia, whereas the peripheral effects may predominate when higher doses or rapidly injected loading doses are administered because of the stimulation of the α_{2B}-adrenoceptor subtype.[21] This idea was confirmed recently by the IV combination of a peripheral α_2-adrenoceptor antagonist (L-659, 066) with a dose (10 $\mu g \cdot kg^{-1}$) of DMED, which attenuated the cardiovascular effects typically associated with DMED alone while still producing the expected level of sedation.[22] Despite this observation, our study demonstrated a dose dependency in intensity and duration of cardiovascular effects. The persistent increase in MAP for the 1.0-$\mu g \cdot kg^{-1} \cdot h^{-1}$ dose (Figure 1) was related to the individual response of two of four tested dogs (note the high variability [SD] of results after MED administration for this dose in Table 1), which did not show such a response in subsequent evaluations (data not shown) when receiving the same MED dose under ISO anesthesia. Technical difficulties with the arterial line or an insufficient level of anesthesia may explain the results for these two dogs. Altogether, at low doses, the hemodynamic effects studied here were small and transient, even disappearing before the end of the CRI administration period. The peripheral vasoconstriction resulting from an α_{2B}-induced increase in SVR was very limited in intensity and duration at the three lowest dosages (0.2, 0.5, and 1.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$). This pharmacologic action governs the increase in MAP and contributes to the bradycardic response, leading to reduced CI. Particularly evident at these low doses, the reduction in HR lasted longer than effects on other hemodynamic parameters. This persistent bradycardia was reported previously in dogs,[3] even at low serum concentrations (<3.9 $ng \cdot mL^{-1}$), and it has been theorized that it may be related to stimulation of central α_{2A}-adrenoceptors.[23] Taken together, these results suggest that low doses of MED CRI during ISO anesthesia in dogs are associated with minimal hemodynamic changes. Whether these low doses also induce efficacious analgesia, muscle relaxation, and sedation remains to be determined.

Four infusion rates (0.2, 1.0, 4.0, and 12.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$) of MED in this study were extrapolated from DMED infusion rates and published pharmacokinetic and pharmacodynamic data.[3,4,11,24] Two intermediate doses (0.5 and 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were added to accurately quantify the dose-dependent nature of the hemodynamic effects. The aim of the highest dose level was to provide a positive control, producing clinically significant cardiovascular effects. Within each group, the total MED doses given during the loading and maintenance CRI periods were equal, and it appears clear that the loading doses were responsible for the dose-dependent effects on cardiovascular function that were noted. In the present study, in contrast to the conclusions derived from data in conscious dogs,[5] increasing the dose not only prolonged the duration of drug effects but also influenced the magnitude of the cardiovascular effects in ISO-anesthetized dogs. Whereas the four higher–CRI rate (1.0, 1.7, 4.0, and 12.0

Taken together, these results suggest that low doses of MED CRI during ISO anesthesia in dogs are associated with minimal hemodynamic changes.

μg·kg^{-1}·h^{-1}) groups demonstrated homogenous pharmacokinetics, the two lowest-dose (0.2 and 0.5 μg·kg^{-1}·h^{-1}) groups demonstrated a different pharmacokinetic pattern. The lowest concentration recorded in this study was almost 10 times higher than the lower limit of quantification. Specifically, the lower the rate below 1.0 μg·kg^{-1}·h^{-1}, the greater the dose-normalized plasma concentration. This change in the pharmacokinetic response of MED is evidenced further by a difference in the timing of its peak plasma concentration, with T_{max} = 55 minutes for the two lowest-dose regimens but T_{max} = 15 minutes for the four highest ones. Considering that AUC (area under the curve) is a function of dosing rate and total clearance,[25] this difference in dose-normalized MED concentrations strongly suggests that MED systemic clearance increased with dose and reached a plateau consistent with Michaelis-Menten kinetics. In dogs, MED is metabolized mainly (80% to 90%) by hepatic hydroxylation followed by glucuronidation, involving several biotransformation pathways.[14]

Although an evaluation of the metabolite kinetics of MED was beyond the scope of this study, recent publications provide indirect support for this hypothesis. The phase II glucuronidation of MED is accomplished by different uridine diphosphate glucuronosyltransferases with different affinity, regioselectivity, and stereoselectivity in human and canine liver microsomes, leading to *N*-glucuronidation of LMED and DMED with different kinetics.[26] In addition, an *O*-glucuronidation pathway has been reported for MED.[14] Hence, it is conceivable that at dose rates below 1.0 μg·kg^{-1}·h^{-1}, MED is metabolized by one pathway only, and the activity of other metabolic pathways becomes significant at increased dosages. Alternatively, DMED may require chiral conversion to LMED to be *N*-glucuronidated at low doses. However, with increasing racemic dose, DMED may be involved in direct *N*-glucuronidation, which would hasten the elimination of MED. This is supported by an earlier report stating that clearance of LMED is more rapid than that of DMED or racemic MED in dogs.[3] Another hypothesis is grounded on the phenotypic polymorphism of the cytochrome P-450–catalyzed phase I hydroxylation of MED, a feature reported in rabbits.[27] If such a polymorphism does exist in dogs, it would induce more rapid biotransformation of MED and different systemic exposure to the drug. We have completed an in vitro study of the metabolic pathways of MED with canine hepatic microsomes, the results of which indicate the drug is subject concurrently to several metabolic pathways implicating at least four different cytochrome P-450 isoenzymes. These results will be presented in a separate manuscript.

This study demonstrated a dose-dependent effect on pH, which was not shown in earlier studies, indicating a further advantage of decreasing the MED CRI dose below the level of potential metabolic acidosis induction.

In contrast to a report from Dutta et al[24] in humans, we did not observe the pharmacodynamic alteration of MED clearance with increasing dose. Dutta et al used pharmacokinetic/pharmacodynamic modeling to show that

CO and hepatic blood flow depression induced by MED decreased the hepatic clearance of MED. This discrepancy in observation may be explained by the major species differences in MED metabolism[28] and the possible interference of ISO anesthesia with MED-induced hemodynamic effects.

Metabolic acidosis, which was reported in earlier studies with MED and DMED,[13,29] was found sporadically at the highest dosage rates used in the current study. Because lactate-free fluids were administered in our study and in the study from Uilenreef et al,[13] the possibility of hyperchloremic acidosis was verified and changes in arterial or venous concentrations of chloride were not demonstrated (data not shown). Furthermore, in our study, this effect was apparent only with higher doses, which also argues against fluid-induced acidosis. In this study, blood gas measurements did not extend beyond MED administration. However, based on previous reports, the magnitude of this acidosis is not clinically relevant.[29] This study demonstrated a dose-dependent effect on pH, which was not shown in earlier studies, indicating a further advantage of decreasing the MED CRI dose below the level of potential metabolic acidosis induction.

Arterial oxygen tension (Pa_{O_2}) during 100% oxygen administration was high, as expected, at all dose regimens. Venous oxygen tension (Pv_{O_2}) decreased significantly during administration of the three highest doses, and this decrease had a dose-dependent tendency even though there were no statistically significant differences among these doses. This finding implies that oxygen extraction increased during higher MED doses, which is consistent with a prior report with DMED.[12] The underlying cause may be decreased CI and peripheral blood flow. Our study was minimally invasive, and the dogs were instrumented with peripheral cannulas only. Thus, central mixed venous blood samples were not available and oxygen consumption and extraction could not be calculated accurately. However, based on the results available, the extraction of oxygen appears to increase in a dose-dependent manner, which was not reported previously with MED or DMED. Although the oxygen balance would remain positive with increasing doses while oxygen extraction is increased,[12] these results indicate a further advantage of using low-dose MED CRI compared with higher doses.

Arterial and venous values of pH, P_{CO_2}, HCO_3^-, glucose, and lactate remained within clinically acceptable ranges during each dose of MED CRI and were consistent with previous findings.[11,12] Venous values of pH, Pv_{CO_2}, HCO_3^-, glucose, and lactate showed results comparable with arterial values, with normal arteriovenous differences; thus, only arterial values are reported in Table 2. However, plasma glucose levels are expected to increase with MED administration because of this agent's ability to inhibit insulin release from the pancreas.[30] This was not demonstrated in our study, probably because samples were not taken beyond the end of infusion. MED has been found to produce slow (i.e., peaks in 2 to 4 hours after administration) and nonsignificant changes in plasma glucose concentrations.[31,32] Arterial lactate concentrations remained within the normal physiologic range (<2.5 $mmol \cdot L^{-1}$) with all dose regimens. This finding was consistent with those from recent reports with DMED during anesthesia,[11,13] implying that the overall tissue perfusion was maintained during our study. Again, in our study, lactate measurement did not continue after MED CRI; thus, lactate retention during CRI may have occurred. Based on a previous study, some lactate retention may occur when the DMED CRI dose is increased to 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$,[13] but it was not demonstrated with lower doses. Thus, it may be speculated that lactate retention

should not occur with low doses of MED CRI either.

With regard to the multitude of possible clinical uses of low-dose DMED CRI in human patients[21,33] and the increasing volume of promising studies being published, the full application of MED or DMED soon may be realized in the veterinary domain. Potential indications for MED or DMED CRI in veterinary patients include use as an adjunct to balanced anesthesia to enhance perioperative hemodynamic stability, as an adjunct to perioperative multimodal analgesia, and as a sedative-analgesic for use in intensive care units.

CONCLUSION

These results demonstrate the dose dependency of the hemodynamic effects of MED CRI when used as an adjunct to ISO anesthesia in dogs. The low-dose MED CRI rates (0.2 to 1.7 $\mu g \cdot kg^{-1} \cdot h^{-1}$) induced limited and transient hemodynamic effects and showed fewer changes in pH and oxygen extraction compared with higher doses. Thus, low-dose MED CRI may prove clinically useful in the perioperative management of canine patients. Further studies are warranted to demonstrate and quantify the efficacy of such CRI doses as analgesic and anesthetic adjuncts. This is particularly important because the correlation between the pharmacodynamic effects and serum MED concentrations may not be linear at all dose rates, as suggested by the data presented here.

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