RESEARCH PAPER

Cardiovascular effects of epidural administration of methadone, ropivacaine 0.75% and their combination in isoflurane anaesthetized dogs

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Abstract

Objective To compare the cardiovascular effects of four epidural treatments in isoflurane anaesthetised dogs.

Study design Prospective, randomized. experimental study.

Animals Six female, neutered Beagle dogs (13.3 ± 1.0 kg), aged 3.6 ± 0.1 years.

Methods Anaesthesia was induced with propofol (8.3 ± 1.1 mg kg^{-1}) and maintained with isoflurane in a mixture of oxygen and air [inspiratory fraction of oxygen (FiO_2) = 40%], using intermittent positive pressure ventilation. Using a cross-over model, NaCl 0.9% (P); methadone 1% 0.1 mg kg^{-1} (M); ropivacaine 0.75% 1.65 mg kg^{-1} (R) or methadone 1% 0.1 mg kg^{-1} + ropivacaine 0.75% 1.65 mg kg^{-1} (RM) in equal volumes (0.23 mL kg^{-1}) using NaCl 0.9%, was administered epidurally at the level of the lumbosacral space. Treatment P was administered to five dogs only. Cardiovascular and respiratory variables, blood gases, and oesophageal temperature were recorded at T-15 and for 60 minutes after epidural injection (T0).

Results Mean overall heart rate (HR in beats minute^{-1}) was significantly lower after treatment M (119 ± 16) ($p = 0.0019$), R (110 ± 18) ($p < 0.0001$) and RM (109 ± 13) ($p < 0.0001$), compared to treatment P (135 ± 21). Additionally, a significant difference in HR between treatments RM and M was found ($p = 0.04$). After both ropivacaine treatments, systemic arterial pressures (sAP) were significantly lower compared to other treatments. No significant overall differences between treatments were present for central venous pressure, cardiac output, stroke volume, systemic vascular resistance, oxygen delivery and arterial oxygen content (CaO_2). Heart rate and sAP significantly increased after treatment P and M compared to baseline (T-15). With all treatments significant reductions from baseline were observed in oesophageal temperature, packed cell volume and CaO_2. A transient unilateral Horner's syndrome occurred in one dog after treatment R.

Conclusions and clinical relevance Clinically important low sAPs were observed after the ropivacaine epidural treatments in isoflurane anaesthetised dogs. Systemic arterial pressures were clinically acceptable when using epidural methadone.

Keywords cardiovascular, dog, epidural, extradural, methadone, ropivacaine.

Introduction

Epidural analgesia is a technique frequently used to achieve adequate preemptive analgesia in veterinary medicine. Many different drugs, including local anaesthetics, opioids, α_2-agonists and ketamine can be administered alone or in combination (Jones 2001). An opioid combined with a long acting local anaesthetic is the most used combination in epidural analgesia (Valverde 2008). Epidural analgesia allows surgical procedures to be performed caudal to the diaphragm in humans and animals, even without the use of general anaesthesia (Heath 1986; Gottschalk & Smith 2001). In dogs however, this is only justified in high risk patients when using adequate monitoring, oxygen supplementation and deep sedation to prevent reaction to external stimuli (Heath 1986). Consequently, epidural anaesthetics and analgesics are most frequently used as an adjunct to general anaesthetic techniques in small animals (Torske & Dyson 2000). Therefore it is of great importance to understand the cardiovascular effects of epidurally administered drugs in isoflurane anaesthetized dogs.

Most clinical studies reporting the cardiovascular effects of long-acting local anaesthetics in dogs have focused on the epidural administration of bupivacaine alone (Hendrix et al. 1996; Torske et al. 1999). However, ropivacaine, a pure S-enantiomer, structurally related to mepivacaine and bupivacaine, is a valuable alternative to bupivacaine, which has induced neurotoxicity, seizures, cardiotoxicity and even cardiac arrest in humans following accidental intravenous (IV) injection (Albright 1979; Casati & Putzu 2005; Leone et al. 2008). Consequently, most studies investigating the cardiovascular effects of ropivacaine, have been designed with a focus on the cardiotoxicity and arrhythmogenic effects of ropivacaine in animals as a model for human medicine (Liu et al. 1982; Feldman et al. 1989; Reiz et al. 1989). The most commonly reported cardiovascular side effect of the epidural administration of local anaesthetics in animals is hypotension (Torske & Dyson 2000), which has been reported after epidural ropivacaine in conscious dogs (Hurley et al. 1991; Duke et al. 2000). To the authors' knowledge no studies have been performed investigating the cardiovascular effects of epidural ropivacaine in isoflurane anaesthetised dogs.

Epidural administration of a small dose of an opioid produces a more profound and prolonged analgesia compared to a full parenteral dose (Skarda 1996). Although morphine remains the classic opioid for epidural techniques in human and veterinary medicine, several other opioids can also be used for this purpose. In humans, epidural methadone has been reported to cause less nausea, pruritus, sedation and urinary retention compared to morphine (Gedney & Liu 1998). Additionally, the incidence of side effects of opioids in dogs is lower after epidural compared to parenteral administration (Valverde et al. 1989). However, information on the epidural use of methadone in the dog is sparse (Jones 2001), and only the effects of extradural and intravenous methadone on isoflurane and postoperative analgesia requirements have been reported in this species (Leibetseder et al. 2006).

The present study was designed to evaluate clinically relevant cardiovascular effects of epidurally administered methadone, ropivacaine 0.75% and the combination of both, in isoflurane anaesthetised dogs.

Materials and methods

Animals

The study received approval from the Ethical Committee of the Faculty of Veterinary Medicine of the University of Ghent (EC 2007/042).

Six female, neutered Beagles, weighing (mean ± SD) 13.3 ± 1.0 kg and aged 3.6 ± 0.1 years, were included in the study. Dogs were classified as ASA (American Society of Anaesthesiologists) class I (normal, healthy patient), based on routine clinical, haematological and biochemical examinations. The dogs were fasted overnight with free access to water, before each experiment.

Anaesthetic and experimental protocol

The dogs were assigned randomly to receive five epidural treatments in a cross over model. A washout period of at least one month was allowed between treatments. The five epidural treatments were: 1) treatment P: NaCl 0.9% (Natrii Chloridum 0.9%, B. Braun, Germany); 2) treatment M: 0.1 mg kg^{-1} of preservative free methadone 1% (Mephenon, Belgium); 3) treatment R: 1.65 mg kg^{-1} of ropivacaine 0.75% (Naropin 7.5 mg mL^{-1}, Astra Zeneca, Belgium); 4) treatment RM: 1.65 mg kg^{-1} of ropivacaine 0.75% combined with

0.1 mg kg^{-1} of preservative free methadone 1%; and 5) treatment HESR: a preload of 7 mL kg^{-1} of hydroxyethylstarch 6% (HAES-steril 6%, Fresenius Kabi n.v., Belgium), administered as a continuous rate infusion over 30 minutes before epidural injection (same treatment as treatment R). The results of the comparison between treatment R and HESR will be published elsewhere (Bosmans et al., in press). All solutions were prepared in equal volumes (0.23 mL kg^{-1}) by addition of NaCl 0.9% as required.

On the day of the experiment a 22 gauge catheter was placed aseptically in a cephalic vein to allow induction of anaesthesia and administration of fluids during anaesthesia. Blood was obtained from a jugular vein, from which plasma sodium concentration (Spotlyte Na/K/Cl Analyzer; Menarini Diagnostics, Italy) and packed cell volume (PCV) (Fisher Bioblock 1-15; Sigma, Osterode, Germany) were measured. PCV was then used to calculate haemoglobin concentration [Hb (g dL^{-1}) = PCV (L L^{-1}) × 34 (Linton et al. 2000)]. The plasma sodium and blood haemoglobin concentrations then were used as required for the Lithium dilution cardiac output monitor (LiDCOplus Haemodynamic Monitor; LiDCO Ltd, UK) in order to measure cardiac output ($\dot{Q}t$).

Anaesthesia was induced with propofol (Propovet, Abbott Animal Health, UK) IV to effect (8.3 ± 1.1 mg kg^{-1}). After endotracheal intubation (7 mm ID cuffed endotracheal tube), anaesthesia was maintained with isoflurane (Isoflo, Abbott Animal Health, UK) in a mixture of oxygen and air such that the fraction of inspired oxygen (FiO$_2$) was 40% and delivered through a rebreathing system (Cicero, Dräger, Germany). End-tidal isoflurane concentration (FE′ISO), was maintained at 1.8% [equivalent to 1.4% MAC, based on a MAC$_{ISO}$ in dogs of 1.3% (Steffey et al. 1994)]. Ringer's lactate solution (Hartmann; Baxter, Belgium) was infused IV at 10 mL kg^{-1} hour^{-1} throughout anaesthesia (up to 60 minutes after epidural injection). Eucapnia (end-tidal carbon dioxide [PE′CO$_2$] between 4.7 and 6.0 kPa) and body temperature were maintained using intermittent positive pressure ventilation (IPPV) and a circulating water heating pad respectively. An intra-arterial 22-gauge catheter was placed aseptically in a dorsal pedal artery, for invasive arterial blood pressure (AP) and cardiac output measurements. Using the Seldinger technique, a 4 Fr central venous catheter (Leader-Cath; Vygon, France) was placed in the right jugular vein with the distal port located in the right atrium. Correct catheter positioning was confirmed by the characteristic pressure waveform. This catheter was used for central venous pressure (CVP) measurement and the bolus injection of lithium chloride (LiDCO Lithium Chloride 0.15 mmol mL^{-1}; LiDCO, UK).

A multichannel physiological monitor (HP M1165A; Hewlett-Packard, Germany) was employed to record the following parameters: electrocardiogram, oesophageal temperature, arterial oxygen saturation (SpO$_2$) (probe placed on the tongue), heart rate (HR), systolic (SAP), diastolic (DAP), and mean arterial blood pressure (MAP) and CVP (during the expiration phase of ventilation). The pressure transducers for AP and CVP (ST-33; PVB Critical Care GmbH, Germany) were calibrated before each experiment using a mercury manometer (Empire N; Rieser, Germany) and were positioned and zeroed at the level of the right atrium. PE′CO$_2$, FiO$_2$, FE′ISO and respiratory rate (f$_R$) were measured using an anaesthetic multigas monitor (Capnomac Ultima; Datex Engstrom Instrumentation, Finland), which was calibrated before each anaesthesia (Quick Cal Calibration Gas; Datex-Ohmeda, Finland). Cardiac output was measured with the lithium dilution technique. The bolus of lithium chloride used was 0.0075 mmol kg^{-1}. Arterial blood samples were collected from the dorsal pedal artery in heparinized syringes for immediate determination of temperature corrected oxygen and carbon dioxide arterial tensions (PaO$_2$ and PaCO$_2$) and pH (ABL-5; Radiometer Medical, Denmark) and of PCV (Haemofuge; Heraeus Instruments, Germany).

After instrumentation, the dogs were positioned in sternal recumbency with the pelvic limbs extended cranially and the head elevated. A stabilisation period of 15 minutes was respected during which the lumbosacral area was aseptically prepared. The cardiovascular measurements were commenced at time point (T) T-15. Total duration of anaesthesia before initiation of the cardiovascular measurements at T-15 (instrumentation period + stabilisation period of 15 minutes) was 49 ± 21 minutes.

At T0, a 22-gauge spinal needle (Yale spinal needle; 1.5 inch, 0.7 × 40 mm, Becton Dickinson, Spain) was introduced into the lumbosacral epidural space with the needle bevel directed towards the sacrum. Correct placement of the needle was confirmed in all dogs by the presence of a distinct 'popping-sensation' as a result of penetrating the *ligamentum flavum*, together with an observed

'tail-flick', the lack of resistance to injection and the absence of cerebrospinal fluid and blood in the needle hub. No attempt was made to aspirate cerebrospinal fluid or blood before injection. The epidural treatment was administered over 2 minutes, while continuously evaluating the resistance to injection to rule out accidental displacement of the needle during drug administration.

Data collection and calculations

Systemic arterial pressures (sAP) (mmHg), SpO_2 (%), oesophageal temperature (°C) and HR (beats minute^{-1}) were recorded at T-15 (baseline measurements), then at T0 and subsequently every 5 minutes for 60 minutes. Blood gases and $\dot{Q}t$ (L minute^{-1}) were obtained at T-15 (baseline measurements), T0, T15, T30, T45 and T60.

The following parameters were calculated (Gross et al. 1990; Lumb 2005):

Stroke volume (SV in mL beat^{-1})

$$= 1000 \times \dot{Q}t \text{ (L minute}^{-1}\text{)/HR (beats minute}^{-1}\text{)}$$

Systemic vascular resistance (SVR in dynes

$$\text{second cm}^{-5}) = [\text{MAP (mmHg)} - \text{CVP (mmHg)}] \times 80/\dot{Q}t$$

Arterial blood oxygen content (CaO$_2$ in mL L^{-1})

$$= [\text{Hb concentration (g L}^{-1}) \times 1.39 \times \text{SaO}_2]$$
$$+ [\text{PaO}_2 \text{ (mmHg)} \times 0.133 \times 0.225]$$

Oxygen delivery ($\dot{D}O_2$ in L minute^{-1})

$$= [\text{CaO}_2 \text{ (mL L}^{-1}) \times \dot{Q}t \text{ (L minute}^{-1})]/1000$$

Statistical analysis

A Shapiro–Wilk's test showed a normal distribution of the data, justifying a parametric statistical approach of the data of this study. An ANOVA-analysis with dog as random effect and treatment as fixed effect was performed to check for differences between treatments at baseline ($\alpha = 0.05$). The effects of the different treatments were compared using a mixed model with dog and period nested in dog as random effect and time, treatment and their interaction as categorical fixed effects. Individual treatments were compared to each other using Tukey's multiple comparisons technique (at global $\alpha = 0.05$). All p-values were adjusted for multiple comparisons.

The effect of time within treatment was investigated comparing the parameter values at each time-point with T-15 (baseline). This analysis was based on a mixed model with dog as random effect and time as categorical fixed effect. Each time point was compared with T-15 using Dunnett's multiple comparisons technique (at global $\alpha = 0.05$). For statistical analysis SAS 9.2 software (SAS 9.2 Windows Version; SAS Institute Inc., NC, USA) was used.

Results

At baseline, no statistically significant differences between treatments were present for any of the observed parameters.

Treatment P was administered to five dogs only, due to the death of one Beagle in treatment HESR. Data from this dog, involving treatment M, R and RM, were not excluded from statistical analysis.

Cardiovascular system

Increases in HR and sAP were observed at the time of placement of the epidural needle in all treatments (except for HR in treatment RM). In four (one, two and one animals in treatment P, M, and R respectively) out of 23 anaesthetic periods (17.4%) this nociceptive stimulation was accompanied by signs of arousal (despite IPPV, spontaneous superficial breathing and tachypnea), requiring administration of a bolus of propofol (0.9 ± 0.4 mg kg^{-1}), to allow continuing IPPV.

Results for the overall comparison between treatments

Overall HR was significantly lower after treatment M, R and RM compared to treatment P, with a mean overall difference of 16 ($p = 0.0019$), 25 ($p < 0.0001$) and 26 ($p < 0.0001$) beats minute^{-1} respectively (Tables 1 and 2). Additionally, overall HR was significantly lower for treatment RM, compared to treatment M, with a mean difference of 10 beats minute^{-1} ($p = 0.04$).

In treatments R and RM, overall SAP, DAP and MAP were significantly lower compared to treatments without ropivacaine (P and M) (Table 1). As an example, overall SAP was significantly lower after treatment R ($p = 0.0027$) and RM ($p = 0.0023$) compared to treatment P, with a mean difference of 40 mmHg for both comparisons.

Table 1 Heart rate (HR), systolic (SAP), diastolic (DAP), mean arterial pressures (MAP), central venous pressure (CVP) and oesophageal temperature, in six dogs anaesthetised with isoflurane (1.4 MAC), receiving one of four epidural injection treatments: saline [P (n = 5)], methadone 0.1 mg kg^{-1} (M), ropivacaine 1.65 mg kg^{-1} (R) and ropivacaine 1.65 mg kg^{-1} + methadone 0.1 mg kg^{-1} (RM) (all equal volumes of 0.23 mL kg^{-1})

	T-15	T0	T5	T10	T15	T20	T25	T30	T35	T40	T45	T50	T55	T60	Overall
HR (beats minute^{-1})															
P	108 ± 24	117 ± 28	126 ± 28	131 ± 26	138 ± 33‡	138 ± 30‡	140 ± 28‡	139 ± 26‡	145 ± 25‡	140 ± 19‡	142 ± 18‡	140 ± 17‡	140 ± 17‡	139 ± 18‡	135 ± 21
M	108 ± 24	119 ± 20	113 ± 16	110 ± 19	115 ± 20	115 ± 21	118 ± 19	119 ± 17	119 ± 15	122 ± 13	125 ± 14‡	126 ± 15‡	130 ± 19‡	130 ± 21‡	119 ± 16*
R	106 ± 15	118 ± 16	106 ± 14	105 ± 21	106 ± 22	109 ± 21	110 ± 20	107 ± 22	108 ± 21	109 ± 22	110 ± 22	116 ± 18	119 ± 17‡	115 ± 20	110 ± 18*
RM	110 ± 18	107 ± 17	101 ± 12	99 ± 9	100 ± 6	104 ± 7	106 ± 10	107 ± 14	109 ± 16	114 ± 21	113 ± 19	116 ± 25	118 ± 28	118 ± 28	109 ± 13*†
SAP (mmHg)															
P	92 ± 11	106 ± 14	116 ± 21‡	120 ± 23‡	125 ± 27‡	128 ± 29‡	135 ± 18‡	139 ± 15‡	146 ± 22‡	148 ± 17‡	142 ± 11‡	142 ± 8‡	142 ± 5‡	142 ± 12‡	130 ± 13
M	81 ± 13	109 ± 21‡	97 ± 16	92 ± 21	103 ± 24‡	112 ± 21‡	118 ± 22‡	123 ± 21‡	124 ± 21‡	124 ± 24‡	126 ± 24‡	132 ± 26‡	135 ± 29‡	135 ± 27‡	115 ± 19
R	88 ± 13	109 ± 25‡	85 ± 15	84 ± 7	84 ± 6	82 ± 6	83 ± 5	85 ± 12	86 ± 12	90 ± 13	92 ± 15	98 ± 14	99 ± 16	102 ± 17	90 ± 10*†
RM	84 ± 15	94 ± 25	80 ± 16	79 ± 28	81 ± 29	80 ± 19	83 ± 22	90 ± 26	94 ± 31	96 ± 28	98 ± 29	96 ± 29	100 ± 30	100 ± 28	90 ± 22*†
DAP (mmHg)															
P	50 ± 6	63 ± 13	68 ± 19‡	72 ± 22‡	75 ± 21‡	76 ± 23‡	81 ± 18‡	84 ± 16‡	86 ± 15‡	87 ± 12‡	86 ± 11‡	86 ± 11‡	84 ± 13‡	84 ± 11‡	77 ± 13
M	47 ± 9	66 ± 13‡	56 ± 10	54 ± 15	62 ± 16‡	63 ± 17‡	67 ± 15‡	70 ± 14‡	71 ± 13‡	74 ± 14‡	75 ± 15‡	73 ± 13‡	73 ± 14‡	73 ± 16‡	66 ± 13
R	47 ± 6	64 ± 16	45 ± 11	46 ± 7	46 ± 5	45 ± 6	46 ± 7	46 ± 10	48 ± 11	49 ± 11	50 ± 13	53 ± 12	54 ± 13	55 ± 14	50 ± 9*†
RM	49 ± 9	59 ± 20	46 ± 10	45 ± 15	47 ± 12	46 ± 9	48 ± 11	52 ± 13	55 ± 17	55 ± 16	58 ± 17	52 ± 13	54 ± 11	54 ± 11	51 ± 10*†
MAP (mmHg)															
P	62 ± 8	75 ± 13	82 ± 3‡	86 ± 24‡	90 ± 24‡	92 ± 25‡	98 ± 19‡	101 ± 16‡	104 ± 16‡	105 ± 13‡	103 ± 11‡	102 ± 10‡	102 ± 10‡	102 ± 11‡	93 ± 14
M	56 ± 10	79 ± 17‡	66 ± 13	63 ± 17	73 ± 19‡	76 ± 19‡	82 ± 17‡	84 ± 16‡	88 ± 16‡	90 ± 16‡	91 ± 17‡	90 ± 16‡	92 ± 18‡	93 ± 19‡	80 ± 15
R	57 ± 6	77 ± 17‡	56 ± 11	54 ± 8	55 ± 6	54 ± 6	56 ± 7	56 ± 11	58 ± 12	59 ± 13	62 ± 14	65 ± 13	67 ± 14	67 ± 15	60 ± 9*†
RM	58 ± 10	65 ± 19	54 ± 11	54 ± 19	56 ± 16	54 ± 11	57 ± 13	62 ± 17	64 ± 20	66 ± 19	66 ± 21	65 ± 19	68 ± 19	67 ± 17	61 ± 14*†
CVP (mmHg)															
P	3.8 ± 3.7	2.4 ± 2.5	1.6 ± 3.0‡	1.8 ± 2.3‡	2.4 ± 3.0	2.4 ± 2.5	2.4 ± 2.5	2.4 ± 2.5	3.0 ± 1.4	2.6 ± 2.1	2.8 ± 2.2	2.4 ± 1.9	2.4 ± 1.9	2.4 ± 1.5	2.5 ± 2.2
M	3.2 ± 1.3	2.7 ± 1.8	2.7 ± 1.4	2.7 ± 1.2	3.2 ± 1.5	3.0 ± 1.4	3.0 ± 1.3	3.3 ± 2.1	3.0 ± 1.8	2.7 ± 2.5	2.5 ± 2.1	2.2 ± 1.9	2.3 ± 1.9	2.5 ± 2.2	2.8 ± 1.6
R	2.7 ± 2.2	2.7 ± 2.2	3.0 ± 2.2	3.2 ± 2.1	2.7 ± 2.2	3.0 ± 1.7	3.0 ± 2.1	3.0 ± 2.0	2.8 ± 2.3	3.2 ± 1.8	3.0 ± 2.1	3.2 ± 2.1	2.8 ± 1.9	2.7 ± 2.2	2.9 ± 2.0
RM	3.8 ± 2.9	2.7 ± 2.0	3.8 ± 1.9	3.8 ± 1.9	3.7 ± 2.1	3.5 ± 2.1	3.3 ± 2.3	3.3 ± 2.3	3.3 ± 2.0	3.0 ± 2.0	2.5 ± 2.1	2.5 ± 2.1	2.7 ± 2.1	2.5 ± 2.1	3.2 ± 1.8
Oesophageal temp (°C)															
P	37.6 ± 0.4	37.4 ± 0.4	37.3 ± 0.3	37.3 ± 0.3	37.3 ± 0.3	37.2 ± 0.3‡	37.2 ± 0.3‡	37.2 ± 0.3‡	37.2 ± 0.4‡	37.2 ± 0.4‡	37.2 ± 0.3‡	37.2 ± 0.4‡	37.2 ± 0.4‡	37.1 ± 0.4‡	37.3 ± 0.3
M	36.9 ± 0.9	36.8 ± 0.8	36.7 ± 0.7	36.7 ± 0.7	36.7 ± 0.6	36.7 ± 0.6	36.6 ± 0.5	36.6 ± 0.5	36.5 ± 0.5	36.5 ± 0.5	36.5 ± 0.5	36.5 ± 0.5	36.5 ± 0.5	36.5 ± 0.6	36.6 ± 0.6
R	37.5 ± 0.6	37.3 ± 0.7	37.3 ± 0.7‡	37.2 ± 0.7‡	37.2 ± 0.7‡	37.1 ± 0.7‡	37.1 ± 0.7‡	37.1 ± 0.7‡	37.1 ± 0.8‡	37.0 ± 0.8‡	37.0 ± 0.8‡	37.0 ± 0.8‡	37.0 ± 0.8‡	37.0 ± 0.7‡	37.1 ± 0.7
RM	37.6 ± 0.9	37.5 ± 0.8	37.4 ± 0.8‡	37.4 ± 0.8	37.3 ± 0.8‡	37.3 ± 0.8‡	37.3 ± 0.8‡	37.2 ± 0.8‡	37.2 ± 0.8‡	37.2 ± 0.8‡	37.1 ± 0.8‡	37.1 ± 0.8‡	37.1 ± 0.8‡	37.0 ± 0.8‡	37.2 ± 0.8

T-15 represents baseline values. T0 represents the end of epidural injection. Data are represented as mean ± SD.
*Significant differences compared to group P for the overall comparison (global α = 0.05).
†Significant differences compared to group M for the overall comparison (global α = 0.05).
‡Significant difference from T-15 within specific treatment (α = 0.05).

Table 2 Cardiac output ($\dot{Q}t$), stroke volume (SV), systemic vascular resistance (SVR), arterial oxygen content (CaO_2) and oxygen delivery ($\dot{D}O_2$) in six dogs anaesthetised with isoflurane (1.4 MAC), receiving one of four epidural injection treatments (see Table 1)

	Time (minutes)						
	T-15	**T0**	**T15**	**T30**	**T45**	**T60**	**Overall**
$\dot{Q}t$ (L minute^{-1})							
P	2.1 ± 0.6	2.2 ± 0.8	2.7 ± 1.6	2.6 ± 0.8	2.9 ± 0.9	3.0 ± 1.1	2.6 ± 0.8
M	1.7 ± 0.6	1.8 ± 0.8	2.0 ± 0.5	2.0 ± 0.9	2.1 ± 1.0	2.3 ± 1.2*	2.0 ± 0.8
R	1.6 ± 0.9	1.8 ± 0.6	1.6 ± 0.4	1.6 ± 0.4	2.0 ± 0.3	2.2 ± 0,3	1.7 ± 0.5
RM	1.6 ± 0.5	1.5 ± 0.5	1.5 ± 0.4	1.6 ± 0.4	1.9 ± 0.5	2.2 ± 0.4*	1.7 ± 0.4
SV (mL beat^{-1})							
P	19 ± 3	18 ± 3	20 ± 8	19 ± 2	21 ± 5	22 ± 7	20 ± 5
M	16 ± 6	15 ± 5	17 ± 2	17 ± 7	17 ± 7	19 ± 8	17 ± 6
R	16 ± 10	16 ± 6	16 ± 6	16 ± 5	20 ± 5	20 ± 4	16 ± 6
RM	15 ± 4	14 ± 5	15 ± 4	15 ± 4	18 ± 5	20 ± 4*	16 ± 4
SVR (dynes second cm^{-5})							
P	2355 ± 537	2900 ± 793	2851 ± 974	3076 ± 495	2882 ± 754	2844 ± 751	2709 ± 589
M	2714 ± 1122	3906 ± 1480	3028 ± 750	3863 ± 2328	4388 ± 3439	3901 ± 2717	3630 ± 1929
R	3856 ± 2915	3666 ± 1531	2936 ± 1276	2815 ± 962	2291 ± 516	2311 ± 406	3193 ± 1552
RM	2841 ± 858	3607 ± 1250	2945 ± 820	3001 ± 997	2789 ± 1234	2158 ± 340	2939 ± 728
CaO_2 (mL L^{-1})							
P	182 ± 15	175 ± 15	170 ± 15	167 ± 16*	166 ± 14*	169 ± 14	172 ± 13
M	187 ± 9	178 ± 17	177 ± 17	170 ± 20*	175 ± 15*	177 ± 13	177 ± 14
R	183 ± 21	177 ± 15	171 ± 18*	167 ± 18*	166 ± 18*	165 ± 19*	172 ± 17
RM	181 ± 14	175 ± 14	166 ± 15*	161 ± 14*	160 ± 16*	158 ± 19*	167 ± 15
$\dot{D}O_2$ (L minute^{-1})							
P	0.37 ± 0.11	0.37 ± 0.15	0.43 ± 0.22	0.46 ± 0.15	0.46 ± 0.11	0.48 ± 0.15	0.44 ± 0.12
M	0.32 ± 0.12	0.32 ± 0.15	0.35 ± 0.12	0.36 ± 0.18	0.38 ± 0.19	0.42 ± 0.22*	0.35 ± 0.15
R	0.30 ± 0.18	0.30 ± 0.10	0.26 ± 0.67	0.26 ± 0.07	0.33 ± 0.05	0.35 ± 0.07	0.29 ± 0.08
RM	0.29 ± 0.08	0.26 ± 0.78	0.24 ± 0.73	0.26 ± 0.06	0.31 ± 0.09	0.33 ± 0.08*	0.28 ± 0.06

T-15 represents baseline values. T0 represents the end of epidural injection. Data are represented as mean ± SD.
*Significant difference from T-15 within the specific treatments (global α = 0.05).

Compared to treatment M, SAP was significantly lower in treatment R (mean difference of 25 mmHg, $p = 0.0355$) and in treatment RM (25 mmHg, $p = 0.0299$). As these differences in systemic arterial pressures gradually increased over time, a significant interaction effect between time and treatment was detected ($p < 0.0001$ for all sAP).

No significant differences between treatments could be observed for mean overall CVP and oesophageal temperature.

No significant differences between treatments were present for mean overall $\dot{Q}t$, SV, SVR, $\dot{D}O_2$ and CaO_2.

Results for the comparison with T-15 within each treatment

After treatments P and M, HR gradually increased and was significantly different from baseline from T15 onwards for treatment P and from T45 onwards for treatment M (Tables 1 and 2). With treatment R, HR increase only reached significance at T55. Heart rate did not change significantly throughout the observational period after treatment RM, although a non-significant decrease in HR was observed from T0–T35.

With treatment P, systemic arterial pressures increased from T0 onwards. The difference with baseline was significant from T5 onwards. The maximum increase was observed at T40 for all sAPs. In treatment M, SAP, DAP and MAP were significantly higher at T0, and from T15 onwards. In treatment R and RM, following the significant increase at epidural injection (T0), then return to baseline measurements, further increases in sAPs were non-significant.

After treatment P, CVP was significantly lower at T5–T10 than at baseline.

A significant increase in $\dot{Q}t$ was observed after treatments M and RM at T60. A significant increase from baseline in SV was observed at T60 in treatment RM only. No significant changes from baseline in SVR were observed in any of the treatments. Arterial oxygen content was significantly lower compared to baseline from T30-T45 after treatments P and M and from T15 onwards after treatments R and RM. Oxygen delivery significantly increased at T60 with treatments M and RM.

Oesophageal temperature decreased over time ($p < 0.0001$) and was significantly lower than at baseline from T20 onwards for treatment P; from T5 onwards for treatments R and RM.

Blood gas analysis and packed cell volume

There were no significant mean overall differences between treatments for any of the arterial blood gases (Table 3). However, a significant interaction effect between time and treatment was detected for arterial pH ($p = 0.0165$). Additionally, arterial pH at T0 was significantly higher than at baseline in treatment RM.

Arterial partial pressure of CO_2 in treatment RM was significantly lower compared to baseline from T0 onwards.

PCV decreased over time in all treatments, and was significantly lower compared to baseline, from T15 onwards after treatments P, R and RM and from T30-T60 after treatment M.

Adverse effects

One dog in treatment R exhibited a transient unilateral Horner's syndrome (HS) on the right side, with ptosis of the upper eyelid and miosis of the affected pupil, after recovering from anaesthesia. The signs gradually disappeared together with disappearance of ropivacaine induced motor block.

Discussion

In the present study, epidural ropivacaine and the combination of ropivacaine with methadone resulted in a lower systemic arterial pressure, compared to epidural injection of saline and of methadone in isoflurane anaesthetised dogs. In contrast, epidural methadone administration was not associated with clinically important cardiovascular changes.

Clear increases in HR and sAP (although not always significantly different from baseline values)

were observed during placement of the epidural needle in all treatments. It was hypothesized that these reactions were mainly a consequence of the lack of premedication, which is routinely used under clinical circumstances as pre-emptive analgesic treatment. As a result, the placement of the epidural needle and the injection, which represented noxious stimuli, induced an increase in sympathetic tone (Lemke 2004). In some dogs, these cardiovascular changes were accompanied by signs of inadequate depth of anaesthesia (such as 'fighting the ventilator'). Consequently, in those dogs the administration of an additional bolus of propofol was necessary to allow continuing artificial ventilation. The administration of a bolus of propofol at the time of epidural needle placement is certainly one of the limitations of the present study, since propofol causes well known cardiovascular effects (Lerche et al. 2000; Auckburally et al. 2008; Enouri et al. 2008). Wouters et al. (1995) described a decrease in MAP of 18% and 45% (for up to 10 and 15 minutes respectively) following induction of anaesthesia with 7.5 and 15 mg kg^{-1} propofol in experimental dogs, together with a decrease in SVR in the high dose group (up to 15 minutes) although $\dot{Q}t$ did not change significantly. Their findings suggest a dose-dependent cardiovascular effect of propofol in non-premedicated dogs, whereby a lower dose produces less cardiovascular depression of shorter duration. The additional doses of propofol used in the present study (0.9 ± 0.4 mg kg^{-1}) were much smaller than the lowest dose reported in the study of Wouters et al. (1995). However, in that study propofol was administered to awake dogs, in contrast to the present study, where isoflurane administration might be expected to accentuate the cardiovascular depressant effects of the administered doses of propofol. Despite this, it appears likely that the additional doses of propofol, administered in the present study, caused only minor and short lasting cardiovascular effects. Additionally, the distribution of the small doses of propofol over the different protocols in the present study was quite similar (one in treatment P, two in treatment M, and one in treatment R), whereby their overall interference with mean values per group was estimated to be relatively low.

Another limitation of the present study was the method used to confirm correct extradural placement of the needle. Dogs were instrumented, ventilated under a stable plane of anaesthesia and maintained on one position making it technically

Table 3 Arterial bloodgases and packed cell volume (PCV) in six dogs anaesthetised with isoflurane (1.4 MAC), receiving one of four epidural injection treatments (see Table 1)

Time (minutes)	T-15	T0	T15	T30	T45	T60	Overall
Arterial blood							
pH							
P	7.34 ± 0.04	7.33 ± 0.02	7.36 ± 0.02	7.33 ± 0.04	7.33 ± 0.03	7.34 ± 0.03	7.34 ± 0.03
M	7.37 ± 0.04	7.37 ± 0.06	7.35 ± 0.04	7.35 ± 0.05	7.34 ± 0.03	7.35 ± 0.03	7.36 ± 0.04
R	7.33 ± 0.05	7.32 ± 0.04	7.33 ± 0.03	7.34 ± 0.04	7.33 ± 0.05	7.35 ± 0.06	7.33 ± 0.04
RM	7.32 ± 0.02	7.35 ± 0.02*	7.33 ± 0.03	7.33 ± 0.02	7.32 ± 0.02	7.32 ± 0.03	7.33 ± 0.02
PCO_2 kPa (mmHg)							
P	5.77 ± 0.71 (43 ± 5)	5.64 ± 0.31 (42 ± 2)	5.16 ± 0.26 (39 ± 2)	4.95 ± 1.04 (37 ± 8)	5.40 ± 0.70 (41 ± 5)	5.24 ± 0.78 (39 ± 6)	5.37 ± 0.60 (40 ± 4)
M	5.83 ± 0.49 (44 ± 4)	5.41 ± 0.79 (41 ± 6)	5.63 ± 0.64 (42 ± 5)	5.61 ± 0.76 (42 ± 6)	5.72 ± 0.73 (43 ± 4)	5.85 ± 0.59 (44 ± 4)	5.69 ± 0.60 (43 ± 5)
R	5.67 ± 0.69 (43 ± 5)	5.63 ± 0.22 (42 ± 2)	5.36 ± 0.61 (40 ± 5)	5.43 ± 0.49 (41 ± 4)	5.30 ± 0.61 (40 ± 5)	5.14 ± 0.57 (39 ± 4)	5.44 ± 0.42 (41 ± 3)
RM	5.85 ± 0.69 (44 ± 5)	5.10 ± 0.50* (38 ± 4)	5.12 ± 0.67* (38 ± 5)*	5.28 ± 0.33* (40 ± 2)*	5.16 ± 0.51* (39 ± 4)*	5.41 ± 0.31* (41 ± 2)*	5.33 ± 0.46 (40 ± 3)
PO_2 kPa (mmHg)							
P	31.84 ± 1.75 (239 ± 13)	32.21 ± 1.74 (241 ± 13)	32.37 ± 1.41 (243 ± 11)	33.28 ± 1.22 (250 ± 9)	33.17 ± 1.12 (249 ± 8)	32.85 ± 1.27 (246 ± 10)	32.62 ± 0.64 (245 ± 5)
M	32.12 ± 2.80 (241 ± 21)	32.61 ± 1.60 (245 ± 12)	32.96 ± 1.57 (247 ± 12)	32.72 ± 1.07 (245 ± 8)	32.25 ± 1.22 (242 ± 9)	31.83 ± 2.42 (239 ± 18)	32.42 ± 1.08 (243 ± 8)
R	31.85 ± 1.69 (239 ± 13)	33.16 ± 1.54 (249 ± 12)	32.74 ± 2.19 (246 ± 16)	32.21 ± 2.81 (242 ± 21)	33.03 ± 2.61 (248 ± 20)	34.42 ± 2.88 (258 ± 22)	32.90 ± 1.67 (247 ± 13)
RM	33.85 ± 2.57 (254 ± 19)	33.21 ± 1.79 (249 ± 13)	32.74 ± 2.30 (246 ± 17)	32.98 ± 1.73 (247 ± 13)	32.56 ± 1.80 (244 ± 14)	30.86 ± 4.32 (231 ± 32)	32.70 ± 1.83 (245 ± 14)
PCV %							
P	37 ± 3	35 ± 3	34 ± 3*	34 ± 3*	34 ± 3*	34 ± 3*	35 ± 3
M	38 ± 2	36 ± 4	36 ± 4	34 ± 4*	36 ± 3*	36 ± 3*	36 ± 3
R	37 ± 4	36 ± 3	35 ± 4*	34 ± 4*	34 ± 4*	33 ± 4*	35 ± 4
RM	37 ± 3	36 ± 3	34 ± 3*	33 ± 3*	32 ± 3*	32 ± 4*	34 ± 3

T-15 represents baseline values. T0 represents the end of epidural injection. Data are represented as mean ± SD.
*Significant difference from T-15 within specific treatment (global α = 0.05).

not possible to confirm correct epidural needle placement radiographically after injection of a radio-opaque contrast agent. However, epidural needles were placed by an experienced person and their placement was accompanied in all dogs by a distinct 'popping-sensation' as a result of penetrating the *ligamentum flavum*, together with a 'tail-flick'. Correct positioning of the needle was tested also by the absence of cerebrospinal fluid and blood at the needle hub and the subsequent 'loss of resistance' to injection of the epidural treatment. In all dogs receiving ropivacaine, paralysis of the hindlimbs was observed during the recovery period after the anaesthetic procedure, thus confirming correct positioning of the needle in these groups. Although different success rates for the 'lack of resistance' method to confirm extradural needle placement have been reported, Iff et al. (2007) achieved 100% correct placement in 18 dogs. In another study, the success rate for experienced anaesthetists was reported to be 95% (in a total of 53 epidurals) (Iff & Moens 2010). Additionally, the loss of resistance test was found to have a specificity of 90% in 54 dogs (Garcia-Pereira et al. 2010), but this study did not specify the experience of the anaesthetist.

After treatment P, HR and sAP gradually increased over time, together with non-significant increases in $\dot{Q}t$, SV and SVR. Although no cardiovascular effects resulting from the placebo epidural treatment were expected, the observed cardiovascular stimulatory effects over time were most likely due to a gradual decrease in the cardiovascular depressant effect of the inhalant agent. Even though the authors could not find evidence for this hypothesis in dogs, a similar effect has been described in spontaneously breathing and mechanically ventilated horses (Dunlop et al. 1987; Steffey et al. 1987a,b; Gasthuys et al. 1990). The uncomfortable position (legs extended cranially in the sternal recumbent dogs) for a long time-period, might be an alternative explanation for the observed cardiovascular stimulatory effects over time in the placebo treatment in the present study.

Leibetseder et al. (2006) reported no significant decreases in median MAP values after epidural administration of 0.3 mg kg^{-1} methadone. In the present study, HR and sAP increased gradually following epidural administration of methadone. These changes were consistently smaller compared to the placebo treatment at comparable time points. Additionally, mean overall HR was lower after

treatment M compared to treatment P, which suggests an effect of epidurally administered methadone on HR. The documented systemic absorption of opioids from the epidural space may explain the cardiovascular changes observed in the present study. With increasing lipophilicity (morphine < methadone < fentanyl), epidurally administered opioids are expected to cause analgesia of faster onset but of shorter duration, because of a more rapid absorption from the epidural space. As a result, effects after epidural administration of lipophilic opioids are similar to those observed after systemic administration (Valverde 2008). The analgesic effect of methadone has been reported to be comparable to IV administration 10 minutes after epidural injection (Leibetseder et al. 2006).

The addition of methadone to the ropivacaine protocol did not induce significant differences in mean overall cardiovascular variables when compared to epidural ropivacaine alone.

Following epidural administration, local anaesthetics may induce hypotension by blocking preganglionic sympathetic efferents, hereby reducing vasoconstrictor activity in affected areas. The degree to which this occurs depends on the balance between sympathetic and parasympathetic activity, the extent of sympathetic block, the effect of systemically absorbed local anaesthetics, the degree of cardiac filling and the adequacy of cardiac function (Veering & Cousins 2000). Additionally, the concurrent administration of anaesthetic drugs, such as inhalant anaesthetics which exert hypotensive effects (Merin et al. 1991) can impair the compensatory haemodynamic response (vasoconstriction in unblocked areas of the body) to neuraxial administration of local anaesthetics (Stanton-Hicks et al. 1975) and result in a greater risk of hypotension in anaesthetized subjects. In the present study, systemic arterial pressures were indeed significantly lower after treatment R and RM compared to treatments P and M. Nevertheless, in the within-treatment comparison with baseline values, no significant decreases in sAP were observed after treatments R and RM. This is in contrast with the study of Hurley et al. (1991), which reported significant decreases in sAP after epidural ropivacaine and bupivacaine in awake dogs. It is probable that, in the present study, epidural ropivacaine did not cause further reductions in arterial blood pressure because baseline values were already low due to the hypotensive effects of isoflurane (Merin et al. 1991). However,

after treatments RM and R, MAP remained below a clinically acceptable level of 60 mmHg (Haskins 1996) for 30 and 45 minutes respectively, whereas cardiovascular function gradually improved over time in treatments P and M. Under clinical conditions, additional fluid therapy, inotropic therapy and dose reduction of isoflurane should therefore be considered to prevent or treat hypotension after epidural ropivacaine administration. In the study of Hurley et al. (1991), $\dot{Q}t$ and CVP decreased, while SV and SVR were not affected. It appears likely that hypotension in those dogs resulted from a decrease in cardiac output and reduction in venous return, as evidenced by a decrease in CVP. In the present study, despite of the use of IPPV, which can cause an additive decrease in venous return (Hartsfield 2007), no significant decrease in CVP was observed. An alternative hypothesis for the lower sAP after both ropivacaine treatments might be an extensive cranial spread of epidurally administered local anaesthetic. However, the expected associated extensive sympathetic block would cause considerable vasodilation, evidenced by a decrease in SVR and CVP, which were not observed in the present study. Despite this, an extensive cranial spread would also explain the presence of a transient unilateral Horner's syndrome in one dog during the recovery. This case has been described in detail elsewhere (Bosmans et al. 2009). Such cranial spread can result in a block of cardiac sympathetic fiber activity to the heart, which is translated in small, but significant changes in heart rate (Otton & Wilson 1966). In the present study, HR was indeed significantly lower after both ropivacaine treatments than after saline injection. This probably contributed to the low values for $\dot{Q}t$ (and therefore sAP) observed after ropivacaine administration. A more extensive cranial distribution of the local anaesthetic in the epidural space can be caused by rapid administration, volume overdosing, inadvertent subarachnoidal injection, a high water solubility of the drug and anatomical changes in the epidural space (Skaredoff & Datta 1981; Lee et al. 1989; Haskins 1992; Torske & Dyson 2000; Narouze et al. 2002). Ropivacaine is more hydrophilic than bupivacaine, so a cranial spread in the extradural space is more likely to occur (Lee et al. 1989). Hurley et al. (1991) observed a similar significant reduction in HR following epidural ropivacaine, but not bupivacaine administration, which is suggestive for a greater cranial spread of ropivacaine.

In the present study, no significant decreases in SVR over time were observed following epidural ropivacaine administration. This is in agreement with the observations of Hurley et al. (1991). Since all dogs receiving epidural ropivacaine in the present study were paralyzed in the hind limbs following anaesthetic recovery, epidural administration of ropivacaine was confirmed. Therefore it can be concluded that epidural ropivacaine did not elicit a significant decrease in sympathetic tone at the dose and volume used in this study.

The blood loss in the present study, due to the lithium dilution cardiac output measurements was estimated to be between 30 and 40 mL per anaesthetic period. The significant decrease in CaO_2 observed in all treatments in the present study, was most probably induced by the concurrent decreases in PCV at respective time points, since PaO_2 and SaO_2 always remained within the expected range.

The drop in oesophageal temperature occurred most quickly in the ropivacaine treatments. A possible cause for this rapid fall is the vasodilation in the area blocked by local anaesthetic.

Unfortunately, one dog was euthanized following unsuccessful resuscitation after complications during treatment HESR. In this dog, severe hypotension was observed immediately following epidural injection. Although cardiovascular function improved upon discontinuation of anaesthesia, the dog did not regain consciousness, nor spontaneous breathing, despite resuscitation attempts lasting for 10 hours. Although uncertain, the cause of death may have been related to the treatment protocol, which included IV hydroxyethylstarch 6% and epidural ropivacaine administration, and the possibility exists that this injection was accidentally administered in the subarachnoidal space. However, as the results from treatment HESR are not part of the present report, details are described and possible causes discussed elsewhere (Bosmans et al., in press). Although the animal did not receive the placebo treatment, the data from the other three treatments in this dog were not excluded, since the applied mixed model procedure conveniently corrects for missing values in the set up of an experiment (Duchateau & Janssen 1997).

In conclusion, epidural administration of ropivacaine (1.65 mg kg^{-1} in a total volume of 0.23 mL kg^{-1}) and the combination of ropivacaine and methadone (1.65 mg kg^{-1} + 0.1 mg kg^{-1} respectively, in equal volume) in ventilated, isoflurane anaesthetised dogs (F$_E'$ISO 1.8%), did not

further aggravate pre-existing hypotension, but initially resulted in clinically important low sAPs with a delayed return to normotension, compared to epidural saline (equal volume) or methadone (0.1 mg kg^{-1}, in equal volume) administration. However, in a clinical setting, a successful epidural technique would lead to lowering of the inhalant vaporizer setting, resulting in decreased haemodynamic effects of the inhalant agent, which might compromise to a lesser degree the compensatory mechanisms responsible for minimising the effect of local vasodilation on systemic blood pressure. Epidural methadone (0.1 mg kg^{-1}, in equal volume) was not associated with clinically important cardiovascular changes.

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