Veterinary
Anaesthesia and Analgesia
Formerly the Journal of Veterinary Anaesthesia

Veterinary Anaesthesia and Analgesia, 2009, **36**, 369–383 doi:10.1111/j.1467-2995.2009.00461.x

RESEARCH PAPER

Clinical evaluation of the efficacy and safety of a constant rate infusion of dexmedetomidine for postoperative pain management in dogs

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Abstract

Objective To compare postoperative analgesia provided by a constant rate infusion (CRI) of dexmedetomidine (DMED) to that of a well-established positive control [morphine (MOR)] in critically ill dogs. The sedative, cardiorespiratory effects and clinical safety of a 24-hour DMED CRI were also evaluated.

Study design Prospective, randomised, blinded, positive-controlled parallel-group clinical study.

Animals Forty hospitalised, client-owned dogs requiring post-operative pain management after invasive surgery.

Methods After surgery, a loading dose of either DMED (25 μg m^{-2}) or MOR (2500 μg m^{-2}) followed by a 24-hour CRI of DMED (25 μg m^{-2} $hour^{-1}$) or MOR (2500 μg m^{-2} $hour^{-1}$) was administered. Pain was measured using the Short Form of the Glasgow Composite Measure Pain Scale, sedation and physiological variables were scored at regular intervals. Animals considered to be painful received rescue analgesia and were allocated to a *post-rescue* protocol; animals which were unresponsive to rescue analgesia were removed from the study. Data were analysed with ANOVA, two-sample *t*-tests or Chi-square tests. Time to intervention was analysed with Kaplan–Meier methodology.

Results Forty dogs were enrolled. Twenty dogs (9 DMED and 11 MOR) did not require rescue analgesia. Eleven DMED and eight MOR dogs were allocated to the *post-rescue* protocol and seven of these removed from the study. Significant differences in pain scores between groups were not observed during the first 12 hours, however, DMED dogs were less ($p = 0.009$) painful during the last 12 hours. Sedation score over the entire 24-hour study was not significantly different between groups.

Conclusion / Clinical Relevance Dexmedetomidine CRI was equally effective as MOR CRI at providing postoperative analgesia and no clinically significant adverse reactions were noted. This study shows the potential of DMED to contribute to a balanced postoperative analgesia regimen in dogs.

Keywords constant rate infusion, dexmedetomidine, dog, morphine, pain.

Introduction

Provision of optimal pain management and control of anxiety in critically ill animals experiencing acute

pain remains a challenge. Opioids are currently considered the gold standard for the treatment of postoperative moderate to severe pain in dogs (Lucas et al. 2001; Kukanich et al. 2005a,b; Guedes et al. 2007). However, administration of high doses of mu agonists can result in excessive sedation or excitation and dysphoria (Hofmeister et al. 2006). In addition, some animals remain painful despite the administration of increased or more frequent doses of opioids.

Combining different classes of analgesic drugs and administering them concurrently is a recognised method of improving perioperative pain management, termed multi-modal analgesia (Jin & Chung 2001; Muir & Woolf 2001). Multi-modal techniques incorporating opioids may also allow a reduction in the total opioid dose required and therefore side effects associated with this class of drug.

Alpha-2 adrenergic receptor agonists (alpha-2 agonists) are commonly used in small animal anaesthesia because of their sedative, anxiolytic (Bloor et al. 1992; Cullen 1996; Hall et al. 2000; Kuusela et al. 2001a,b) and analgesic effects (Vainio et al. 1989; Barnhart et al. 2000; Grimm et al. 2000). However, they are not commonly used solely for provision of analgesia as a result of concerns regarding cardiovascular side effects and concurrent sedation. The analgesic effect provided by a single dose of medetomidine (MED) is of shorter duration than sedation (Kuusela et al. 2000, 2001b), necessitating re-dosing at frequent intervals in order to ensure an adequate level of analgesia.

Constant rate infusion (CRI) techniques are superior to intermittent re-dosing schemes for many analgesic and anaesthetic drugs (Urquhart 2000; Lucas et al. 2001). They are better able to maintain plasma drug concentration within the target therapeutic range, avoiding peaks and troughs in plasma drug concentration and therefore variability in drug effect. Dexmedetomidine (DMED) CRI has been evaluated as an adjunct to anaesthesia in dogs, both in clinical (Uilenreef et al. 2008) and experimental studies (Pascoe et al. 2005; Lin et al. 2008). However, the potential of CRI DMED to contribute to a balanced analgesia regimen, for postoperative pain management, in dogs requiring intensive analgesia therapy has not been previously investigated.

In humans, DMED is approved for short duration (<24 hours) sedation in the intensive care unit (ICU) or operating theatre settings (Venn et al. 1999; Ebert et al. 2000; Hall et al. 2000; Venn & Grounds 2001; Shehabi et al. 2004; Tobias & Berkenbosch 2004). DMED has also undergone limited evaluation in humans for the provision of postoperative analgesia and has been shown to improve patient comfort and analgesia when administered concurrently with opioids, compared to the administration of opioids alone (Arain et al. 2004; Unlugenc et al. 2005). DMED CRI also reduced the requirement for opioid analgesia and, thereby, reduced side effects associated with opioid administration in humans.

The aim of the present investigation was to compare postoperative analgesia provided by a CRI of morphine (MOR) or DMED in dogs referred for invasive surgery at Utrecht University. Both drugs were administered for 24 hours after surgery, rescue analgesia was provided in animals deemed to be painful during the study period. Our hypothesis was that the analgesia provided by DMED would be as good as or better than MOR. Pain, sedation, and cardiovascular parameters were measured throughout the study period.

Materials and methods

Animals

The study was approved by the Committee for the Ethical Care of Animals of the Utrecht University. Informed owner consent was obtained prior to enrolment of all dogs in the study.

Client-owned dogs of any breed and of either sex (neutered or intact) presented to the Department of Clinical Sciences of Companion Animals (DCSCA), University Utrecht for surgical procedures requiring intensive postoperative pain management were considered for inclusion in this study. Intensive postoperative pain management was defined as pain for which intermittent treatment with a mu opioid agonist (e.g. MOR or methadone) would be indicated for at least 24 hours after surgery. Types of procedure included exploratory laparotomy, thoracotomy or orthopaedic surgery. Other surgical procedures were considered on a case by case basis. Before final enrolment the dogs had to fulfil a set of predetermined inclusion and exclusion criteria (Table 1).

Of the 40 dogs that entered the study, nine were crossbred and 31 were purebred. Breeds were represented by one or two dogs each, with exception of German Shepherd (n = 5; DMED 1, MOR 4) and

Table 1 Enrolment criteria for dogs to enter the study

Body weight ≥2 kg
Age ≥12 weeks
Postoperative care requires intensive[1] postoperative analgesia
Administration of 0.3 mg kg^{-1} morphine IM at the end of the surgery for the purpose of facilitating recovery and transfer to the ICU
Oral or written owner consent
No previous enrolment in this study
No evidence or history of pre-existing heart disease or clinically significant arrhythmia
No clinically significant hypotension
No evidence or a history of liver disease
No evidence or a history of neurological disease or a change in neurological status as a result of the surgery
No history of hypersensitivity to alpha-adrenergic agonists or morphine
Not too aggressive to safely enable postoperative examination and/or pain scoring.
Not ASA category 5
Not pregnant or lactating
No administration of non-steroidal anti-inflammatory drugs, epidural analgesia, or local/regional analgesia within 12 hours prior to the study
No administration of inotropic drugs during the last 15 minutes of general anaesthesia

ASA, American Society of Anaesthesiologists.
[1]See text for definition.

Table 2 Animal disposition and demographics for the DMED and MOR groups

Parameter	DMED	MOR	Total
Purebred/ Crossbred	14/6	17/3	31/9
Age (years)	06.7 ± 3.1	5.3 ± 3.4	6.0 ± 3.3
Male (neutered)	9 (3)	13 (3)	22 (6)
Female (neutered)	11 (5)	7 (4)	18 (9)
Body weight (kg)	27.8 ± 15.8	26.8 ± 13.0	27.4 ± 14.3
ASA category 2–3–4	3–13–4	1–10–9	4–23–13
Surgery			
Abdominal	14	18	32
Thoracic	6	1	7
Spinal neurosurgery	0	1	1
Duration of surgery (minutes)	125 ± 44	121 ± 56	123 ± 50

DMED, dexmedetomidine; ASA, American Society of Anaesthesiologists; MOR, morphine.

Labrador Retriever (n = 4; DMED 2, MOR 2). The dogs [18 females (9 neutered), 22 males (6 neutered)] had a median age of 6.8 years (range 0.3–11.4 years) (Table 2).

Study design and drugs

The study was carried out at the ICU of the DCSCA and was designed as a randomised, positive-controlled, blinded parallel-group, non-inferiority, clinical trial. The study was run by a single investigator. Forty dogs were randomly allocated to one of two treatment groups, MOR or DMED CRI. Treatment unblinders (scratch cards) were provided to the investigator for the purpose of unblinding of a study animal only in case of emergency.

Intra-operative analgesia and anaesthetic management

The anaesthetic management of dogs recruited to the study was not standardized and was determined by the ASA status of the animal and surgical procedure. However, all animals received a CRI of sufentanil (Sufentanil-Hameln 5 μg mL^{-1}; Hameln Pharmaceuticals Gmbh, Hameln, Germany) during surgery in combination with isoflurane for maintenance of anaesthesia. All dogs enrolled in the study received MOR IM (0.3 mg kg^{-1}) approximately 30 minutes prior to the end of anaesthesia and surgery.

At the end of surgery dogs were transferred from the operating theatre to the ICU. Before final enrolment in the study animals' tracheas were extubated and the animals given a brief clinical examination to reconfirm that they met the inclusion and exclusion criteria for the study. Between 10 and 30 minutes after extubation dogs in the DMED treatment group (DMED group) (n = 20) received at T 0 minutes a loading bolus of DMED [Dexdomitor; (diluted to 4 μg mL^{-1}); Orion Pharma, Espoo, Finland] of 25 μg m^{-2} (equivalent to 1 μg kg^{-1} for an average 16 kg dog) by slow intravenous (IV) injection, immediately followed by a CRI (25 μg m^{-2} $hour^{-1}$) for 24 hours. Dogs in the MOR treatment group (MOR group) (n = 20) received at T 0 minutes a loading bolus of MOR (Morphine hydrochloride (diluted to 400 μg mL^{-1}); BUFA b.v., Uitgeest, the Netherlands) of 2500 μg m^{-2} (equivalent to approximately to 0.1 mg kg^{-1} for an average 16 kg dog) IV bolus by slow IV injection, immediately followed by a CRI of 2500 μg m^{-2} $hour^{-1}$ (equivalent to 0.1 mg kg^{-1}

hour^{-1} for an average 16 kg dog). Each bottle containing the study drugs was labelled with the study code and with the animal's study number (1–20). The content was colourless and odourless and the dilution of the drugs (either MOR or DMED) was performed by the ISO 9001–2001 certified Utrecht University Pharmacy with a standardized procedure so that the amount in milliliters required by every animal was calculated on its weight and was the same for both drugs.

Procedures and instrumentation

While the dog was anaesthetised an intravenous catheter (Vasofix Braunüle; B. Braun Melsungen AG, Melsungen, Germany) was placed in the cephalic vein for administration of the test drug CRI using a syringe pump (Perfusor FM; B. Braun Melsungen AG, Melsungen, Germany). A jugular vein was catheterized (Certo Splittocan or Certofix Mono Paed; B. Braun Melsungen AG, Melsungen, Germany) for measurement of central venous pressure (CVP) and administration of fluids and concomitant medications. The dorsal pedal artery was catheterized (Arterial Cannula with FloSwitch; Becton Dickinson, Swindon, UK) and connected to a transducer (Gabarith PMSet 1DT-XX Rose; Becton Dickinson, Singapore) for measurement of arterial blood pressure.

When the dog was returned to the ICU adhesive foam electrodes (Meditrace 530; Tyco Healthcare, Chicopee, MD, USA) were applied to the chest and connected to a transmitter (Cardiac Telemetry System WEP-8430, Nihon Kohden Corp., Tokyo, Japan) bandaged to the chest wall to record the electrocardiogram (ECG). A urinary catheter (Arnolds AS89; SIMS Portex Ltd., Hythe, UK) was placed via the urethra into the urinary bladder and connected to a closed collection system. Other interventions in recovery included delivery of supplementary oxygen via a nasal oxygen cannula connected to a closed oxygen delivery system set at 50–100 mL minute^{-1}. Rectal temperature (RT) was monitored regularly and maintained between 37 and 39 °C with either a heating lamp or a warm-air blanket (BairHugger Total Temperature Management System; Arizant Healthcare Inc., Eden Prairie, MN, USA).

Intravenous fluid therapy was provided according to the standard principles for maintenance or corrective fluid therapy routinely applied in the ICU. Fluids were administered with the aid of volumetric or syringe pumps (Infusomat or Perfusor FM; B. Braun Melsungen AG, Melsungen, Germany). Water was available postoperatively provided the dog was able to demonstrate a sufficient swallowing reflex. Food was generally withheld during the postoperative study period. However, in the event of specific, postoperative requirements either enteral or parenteral feeding was initiated.

Data collection

Within 10–30 minutes of endotracheal extubation and at least 45 minutes after the intra-operative dose of MOR, baseline (T−5 minutes) data collection was initiated. Relative to bolus treatment injection (T0 minutes), data were collected at T−5, 30, 60, 90 and 120 minutes (±30 seconds) and then at T−4, 8, 12, 16, 20, and 24 hours (±5 minutes) in the following order: heart rate (HR) and heart rhythm (ECG), respiratory rate ($_f$R), cumulative fluid administration (cFA), cumulative urine production (cUP), arterial blood pressure [mean, systolic and diastolic (MAP, SAP and DAP)], subjective sedation score (SED) (Granholm et al. 2007), Glasgow Composite Measure Pain Scale score (CMPS-SF) (Reid et al. 2007), pedal withdrawal reflex (PED) score, mucous membrane colour (MM), capillary refill time (CRT), CVP and RT. At T6 and 10 hours, only sedation, pain and PED score were assessed. During pain assessment section B of the CMPS-SF (concerning the dogs ability to stand and walk) was omitted, as this section could not be assessed at all time points. A total pain score ranging from 0 to 20 was calculated for each time point.

The dog's PED was subjectively assessed by pinching the interdigital skin of a hind foot. The score ranging from 0 to 3 with a numerical rating scale was calculated at each time point (Granholm et al. 2007).

Heart rate and rhythm were obtained from a 30-second electrocardiogram (ECG) recording printed from the telemetry apparatus (Cardiac Telemetry System WEP-8430, Nihon Kohden Corp., Tokyo, Japan). ECG recordings were evaluated by an independent blinded veterinary cardiologist for the presence or absence at each time point for 1° and 2° atrioventricular (AV) block, sinus arrhythmia, sinus pause, lengthened Q-T interval, supraventricular (SVPC) and ventricular (VPC) premature complexes or any other rhythm abnormalities.

Arterial blood pressures (MAP, DAP and SAP) were collected from the anaesthetic monitor

(Datex AS/3; Datex, Helsinki, Finland). CRT was subjectively scored [0 = ≤1.5 seconds (normal); 1 = >1.5 seconds (prolonged)] and MM was subjectively scored (0 = normal, 1 = pale, 2 = cyanotic, 3 = hyperaemic). CVP was determined by measurement with a water manometer system connected to the jugular catheter with the dog in lateral recumbency. RT was measured with a rectal thermometer.

Adverse events were recorded at any time during the study according to good clinical practice guidelines. The investigator discontinued the CRI if she observed that the dog needed to defecate outside of the cage. The time of CRI discontinuation and restart of the CRI was recorded. The CRI treatment was discontinued immediately after T 24 hours; the end volume of CRI administered and time were recorded.

Rescue medication protocol

Rescue medication (0.2 mg kg^{-1} MOR IV) was administered if a dog was observed with significant postoperative pain (pain score of ≥5 as determined by the CMPS-SF) at any time during the study.

Following the first administration of rescue medication the dog entered a different protocol called the '*post-rescue*' protocol. In this group of animals collection of experimental data continued for a total of 24 hours after administration of the MOR or DMED bolus, but the time schedule was reset with 'T-0 *post-rescue*' being the time the first rescue MOR bolus was administered. A new data collection sheet was used for these patients. Data were assessed at T15, 30, 45 (CMPS-SF only), 60, 90 and 120 minutes (±30 seconds) and then at T4, 8, 10, 12, 16, 20, and 24 hours (±5 minutes) for the same parameters and in the same order as described in the regular protocol.

If a pain score of ≥5 was observed at T15 minutes in animals that had entered the *post-rescue* protocol, a second MOR bolus was administered. Fifteen minutes later pain was re-evaluated and if a pain score of ≥5 was still observed the dog was considered a treatment failure, the experimental data collection was stopped, and the dog was excluded from the study. When dogs received rescue MOR and a reduction in pain score (≤5) occurred at reassessment, further MOR boluses could be administered hourly if a pain score of ≥5 was observed at later time points. However, if more than one MOR bolus per hour was necessary to control postoperative pain, the dog was also considered a treatment failure. Following removal from the study, the dog was administered supplemental analgesic drugs as deemed necessary.

Concomitant medication

The use of other medication was left to the discretion of the clinician in charge of the dog. Because of the critical status of most dogs during the experiment an exact list of prohibited concomitant treatments could not be formulated. However, the use of the following drugs was prohibited during T0–24 hours: atipamezole or other alpha$_2$-adrenergic antagonists; anti-inflammatory analgesics or pain relieving medications [nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, other alpha$_2$-adrenergic agonists or opioids]; sedatives.

Statistical analysis

A hypothesis statement was written prior to the study as follows: DMED will not be considered clinically inferior to MOR in terms of post-operative analgesia if the pain score for DMED is not more than 3 units greater than MOR. This was studied for three time periods: T0–2 hours, T0–12 hours and T 0–24 hours. A two-sided, 95% confidence interval for the difference between treatments (DMED-MOR) was calculated.

An analysis of variance was conducted for the fixed effects of treatment, time, treatment and time, and the random effect of dog nested within treatment for the following continuous variables: HR, $_f$R, cumulative fluid therapy, cUP, MAP, SAP, DAP, SED, CRT, CVP, and RT. Contrasts between each time point *versus* baseline (T−5 minutes) were also estimated for each treatment. A two-sample *t*-test was used for the fixed effect of treatment for the following continuous variables: age, weight and duration of the surgical procedure, time between extubation and T0, dose of bolus, dose of CRI and total time of CRI. The following variables were analyzed by Chi-square tests which accounted for the treatment [by time point (−5 minutes to 24 hours)]: breed category (crossbreed *versus* rebred), sex (male *versus* female), and ASA category (1 and 2 *versus* 3 and 4), reaction to bolus injection, intervention with rescue medication, PED, MM and the heart rhythms. The time to intervention with rescue medication was analyzed with Kaplan–Meier survival analysis methodology.

Separate analyses were conducted for data obtained after rescue medication administration. An analysis of covariance with the time of intervention as a covariate was conducted. Time points used in these analyses were respective to the time of rescue medication administration (T_{res} 0 minutes). A two-sided, 5% significance level was applied throughout the study and data were expressed as mean ± SD if not indicated otherwise.

Results

Animals

Forty-five dogs were screened for enrolment in the study. Five of these did not enter the study. Three dogs had not received MOR 30 minutes before the end of anaesthesia and two dogs needed inotropic drugs to manage hypotension at the end of anaesthesia.

There were no statistical differences in breed category, sex, age, body weight or type (abdominal, thoracic and spinal neurosurgery) and duration of surgery between DMED and MOR group (Table 2). No animals requiring orthopaedic surgery for fracture repair were included in the study, this reflected the population of animals eligible for recruitment into the study during the period of data collection.

Study outcome

Twenty dogs (11 in the MOR group; 9 in the DMED group) remained enrolled until the end of the study (T24 hours). One dog (MOR group) was withdrawn as a result of mishandling of the CRI. Eight dogs in the MOR group and 11 dogs in the DMED were considered painful (CMPS-SF score ≥5) and required rescue medication administration. These dogs were allocated to the *post-rescue* protocol and data were collected as described. Five dogs, (three DMED group, two MOR group) were considered as treatment failures and removed from the study because they required more than one MOR bolus per hour to control postoperative pain.

Analgesic medication

The DMED or MOR bolus was administered 24.4 ± 9.4 minutes after endotracheal extubation [DMED: 22.9 ± 7.8 minutes; MOR:25.8 ± 10.8 minutes; not significant (NS)]. Animals in the DMED group received a bolus of 25 ± 0.2 μg m^{-2} and were maintained on 24.9 ± 0.8 μg m^{-2} $hour^{-1}$ CRI. Dogs in the MOR group received a bolus of 2506.5 ± 21.3 μg m^{-2} and were maintained on 2445.1 ± 249.8 μg m^{-2} $hour^{-1}$ CRI.

Rescue medication

Rescue MOR was administered 39 times in total (11 DMED and eight MOR dogs ($p = 0.3422$) at a median CMPS-SF score of 7.0 (DMED: median 7 (range 5–13); MOR: median 7 (range 6–8). For the animals that received rescue medication, the time of intervention was 6.1 ± 6.4 hours (DMED: 6.4 ± 5.9 hours; MOR: 5.8 ± 7.4 hours; NS).

Pain, sedation and PED assessment

Significant differences in pain scores between groups were not observed during the first 12 hours. However, DMED dogs were less ($p = 0.009$) painful during the last 12 hours (Table 3). The DMED dogs had significantly higher sedation scores at time points 30, 60, and 90 minutes, but the overall sedation score (24 hours) was not significantly different between groups. Results of the CMPS-SF and SED score over time are summarized in Table 4**.** PEDs were more suppressed in DMED dogs compared to MOR dogs at time points 30 and 60 minutes. The Composite Measure Pain Scale score was significantly lower ($p = 0.0269$) for DMED compared to MOR in dogs allocated to the *post-rescue* protocol (Table 5).

Physiological parameters

Typical alpha-2 agonist mediated cardiovascular changes occurred during administration of the

Table 3 Least square means ± SE CMPS-SF score for three postoperative time periods during continuous rate infusion of DMED or MOR

		Postoperative time period		
Variable	**Group**	**0–2 hours**	**0–12 hours**	**0–24 hours**
CMPS-SF score (0–20)	DMED	2.8 ± 0.3	2.5 ± 0.3	0.9 ± 0.3[b]
	MOR	2.8 ± 0.3	2.9 ± 0.3	1.9 ± 0.3[a]

CMPS-SF, Glasgow Composite Measure Pain Scale score; DMED, dexmedetomidine; MOR, morphine.
[a,b]Significant difference between groups ($p = 0.009$).

Table 4 Means ± SD CMPS-SF and SED at baseline and during a 24-hours postoperative continuous rate infusion of DMED or MOR

Variable	Group	Baseline −5 minutes	During CRI 30 minutes	60 minutes	90 minutes	120 minutes	4 hours	6 hours	8 hours	10 hours	12 hours	16 hours	20 hours	24 hours
CMPS-SF* (score: 0–20)	DMED	4.4 ± 3.0 (19)	2.6 ± 1.4 (20)	2.5 ± 1.0 (19)	2.7 ± 1.8 (19)	2.5 ± 1.2 (16)	2.5 ± 1.4 (15)	2.1 ± 1.1 (14)	2.4 ± 1.1 (12)	2.1 ± 1.4 (11)	2.0 ± 1.3 (10)	0.8 ± 0.6 (10)	1.0 ± 1.2 (10)	0.6 ± 0.5 (9)
	MOR	5.1 ± 3.5 (20)	3.1 ± 1.5 (20)	2.4 ± 1.2 (19)	2.6 ± 1.3 (19)	2.2 ± 1.2 (18)	2.7 ± 1.6 (16)	2.9 ± 1.6 (14)	2.2 ± 0.9 (12)	2.1 ± 1.2 (12)	2.6 ± 1.3 (12)	2.1 ± 1.1 (12)	1.8 ± 1.1 (12)	1.7 ± 0.9 (11)
SED (score: 0–10)	DMED	5.4 ± 2.8 (19)	6.4 ± 2.6[a] (20)	5.6 ± 2.1[a] (19)	5.4 ± 2.0[a] (19)	4.4 ± 2.2 (16)	3.3 ± 1.8 (15)	2.9 ± 1.8 (14)	2.3 ± 1.1 (12)	2.3 ± 1.1 (11)	1.7 ± 1.1 (10)	1.4 ± 1.0 (10)	0.9 ± 0.7 (10)	0.4 ± 0.7 (9)
	MOR	5.6 ± 2.5 (19)	4.4 ± 1.9[b] (20)	3.9 ± 1.8[b] (19)	3.4 ± 1.3[b] (19)	3.2 ± 1.3 (18)	2.9 ± 1.7 (16)	2.1 ± 1.4 (14)	2.1 ± 1.2 (12)	1.8 ± 1.3 (12)	2.0 ± 1.1 (12)	1.8 ± 1.7 (12)	1.0 ± 1.3 (12)	0.9 ± 1.3 (11)

Number of dogs indicated in brackets. CMPS-SF, Glasgow Composite Measure Pain Scale score; DMED, dexmedetomidine; MOR, morphine; SED, sedation score; CRI, constant rate infusion.
*Comparison of groups per time point was not performed.
[a,b]Within a time point, treatments differ ($p < 0.05$).

Table 5 Mean ± SD CMPS-SF and SED after initiation of rescue medication in combination with MOR and CRI of DMED or MOR

Variable	Group	During rescue + CRI 15 minutes	30 minutes	45 minutes	60 minutes	90 minutes	120 minutes	4 hours	6 hours	8 hours	10 hours	12 hours	16 hours	20 hours	24 hours
CMPS-SF (score: 0–20)	DMED*	2.7 ± 1.6 (11)	3.8 ± 1.2 (11)	2.7 ± 1.0 (10)	3.4 ± 1.8 (10)	3.1 ± 2.3 (10)	3.1 ± 1.2 (10)	4.4 ± 2.8 (10)	2.9 ± 1.9 (7)	2.4 ± 1.6 (7)	3.0 ± 1.2 (7)	2.7 ± 1.1 (7)	1.6 ± 1.7 (7)	1.6 ± 1.5 (5)	0.5 ± 0.7 (2)
	MOR	3.6 ± 1.7 (8)	3.8 ± 2.7 (8)	3.6 ± 2.1 (5)	3.6 ± 2.2 (5)	3.0 ± 1.2 (4)	4.0 ± 0.8 (4)	3.5 ± 1.0 (4)	5.5 ± 2.4 (4)	3.3 ± 1.2 (3)	4.0 ± 0.0 (3)	4.0 ± 0.0 (3)	3.3 ± 1.2 (3)	1.7 ± 1.0 (3)	0.6 ± 0.3 (3)
SED (score: 0–10)	DMED		3.8 ± 2.4 (11)		3.4 ± 1.4 (10)	3.4 ± 1.6 (10)	3.2 ± 1.3 (10)	3.1 ± 1.5 (10)	3.0 ± 1.0 (10)	1.9 ± 1.3 (11)	1.4 ± 1.0 (10)	1.9 ± 0.9 (7)	1.3 ± 1.0 (7)	1.4 ± 0.9 (5)	1.0 ± 0.0 (2)
	MOR		2.8 ± 1.4 (8)		4.2 ± 1.1 (5)	4.3 ± 1.0 (4)	4.0 ± 0.8 (4)	3.0 ± 0.8 (4)	2.8 ± 0.5 (4)	2.3 ± 0.6 (3)	2.3 ± 1.5 (3)	1.3 ± 0.6 (3)	2.7 ± 2.1 (3)	1.0 ± 0.0 (3)	1.0 ± 0.0 (3)

Number of dogs indicated in brackets.
CMPS-SF, Glasgow Composite Measure Pain Scale score; DMED, dexmedetomidine; MOR, morphine; SED, sedation score; CRI, constant rate infusion.
*Significant overall effect of treatment ($p = 0.0269$).

Table 6 Physiological parameters (mean ± SD) at baseline and during 24 hours postoperative CRI of DMED or MOR

			During CRI									
Variable	**Group**	**Baseline −5 minutes**	**30 minutes**	**60 minutes**	**90 minutes**	**120 minutes**	**4 hours**	**8 hours**	**12 hours**	**16 hours**	**20 hours**	**24 hours**
HR (beats minute^{-1})	DMED	108 ± 20 (18)	70 ± 20[a] (20)	67 ± 24[a] (19)	68 ± 22[a] (19)	67 ± 22[a] (16)	70 ± 26[a] (15)	79 ± 20 (12)	85 ± 22 (10)	82 ± 25 (10)	90 ± 29 (10)	76 ± 13 (9)
	MOR	105 ± 30 (20)	98 ± 25 (20)	96 ± 30 (19)	98 ± 24 (19)	91 ± 28 (18)	95 ± 31 (16)	79 ± 27 (12)	72 ± 19 (12)	72 ± 31 (12)	73 ± 36 (12)	70 ± 16 (11)
$_{f}$R (breaths minute^{-1})	DMED	26 ± 13 (15)	17 ± 10 (19)	16 ± 7 (17)	17 ± 8 (16)	20 ± 9 (15)	22 ± 13 (14)	28 ± 14 (12)	39 ± 17 (8)	26 ± 7 (8)	27 ± 8 (9)	28 ± 9 (9)
	MOR	22 ± 11 (17)	28 ± 27 (19)	25 ± 12 (15)	27 ± 14 (15)	27 ± 16 (16)	32 ± 17 (14)	26 ± 11 (9)	38 ± 20 (11)	31 ± 15 (11)	28 ± 14 (11)	32 ± 14 (9)
CVP (cmH_2O)	DMED	3.1 ± 3.7[a] (17)	4.7 ± 3.3[a] (20)	4.3 ± 3.1[a] (19)	4.5 ± 2.9[a] (17)	4.5 ± 2.8[a] (16)	3.9 ± 2.7 (15)	3.3 ± 3.0 (12)	3.5 ± 2.3 (10)	3.5 ± 2.4 (9)	3.2 ± 2.2 (10)	3.5 ± 2.2 (9)
	MOR	0.8 ± 2.1 (18)	1.2 ± 1.8 (19)	1.7 ± 1.6 (19)	1.9 ± 1.6 (18)	2.2 ± 1.9 (18)	3.0 ± 2.6 (15)	3.1 ± 1.9 (12)	3.6 ± 1.9 (12)	4.0 ± 2.1 (12)	4.1 ± 1.9 (12)	4.1 ± 1.8 (12)
MAP (mmHg)	DMED	108 ± 21 (17)	102 ± 13 (19)	103 ± 14 (19)	102 ± 17 (19)	101 ± 13 (16)	103 ± 16 (15)	100 ± 12 (12)	100 ± 9 (10)	99 ± 8 (9)	107 ± 19 (9)	105 ± 13 (8)
	MOR	95 ± 15 (17)	93 ± 14 (19)	99 ± 20 (18)	99 ± 16 (18)	97 ± 27 (17)	103 ± 23 (15)	97 ± 11 (11)	95 ± 13 (11)	91 ± 15 (11)	96 ± 15 (11)	94 ± 17 (10)
SAP (mmHg)	DMED	166 ± 27 (17)	153 ± 21 (19)	149 ± 22 (19)	148 ± 22 (19)	145 ± 18 (16)	153 ± 20 (15)	149 ± 15 (12)	145 ± 16 (10)	149 ± 19 (9)	156 ± 19 (9)	154 ± 15 (8)
	MOR	153 ± 40 (17)	147 ± 32 (19)	151 ± 32 (18)	152 ± 30 (18)	163 ± 33 (17)	165 ± 30 (15)	161 ± 16 (11)	156 ± 17 (11)	156 ± 18 (11)	161 ± 17 (11)	154 ± 23 (10)
DAP (mmHg)	DMED*	86 ± 18 (17)	85 ± 13 (19)	82 ± 10 (19)	84 ± 14 (19)	83 ± 12 (16)	84 ± 16 (15)	84 ± 10 (12)	82 ± 6 (10)	80 ± 7 (9)	86 ± 9 (9)	85 ± 11 (8)
	MOR	74 ± 13 (17)	74 ± 13 (19)	76 ± 15 (18)	77 ± 15 (18)	81 ± 15 (17)	78 ± 20 (15)	75 ± 10 (11)	75 ± 14 (11)	74 ± 21 (11)	76 ± 15 (11)	74 ± 17 (10)
RT (°C)	DMED	36.9 ± 0.9 (17)	37. 0 ± 1.0 (20)	37.1 ± 0.8 (19)	37.2 ± 0.7 (18)	37.4 ± 0.6 (16)	37.7 ± 0.6 (15)	38.0 ± 0.5 (12)	38.2 ± 0.4 (10)	38.2 ± 0.5 (10)	38.2 ± 0.5 (10)	38.2 ± 0.4 (9)
	MOR	36.9 ± 1.0 (18)	37.0 ± 0.8 (19)	37.1 ± 0.8 (19)	37.3 ± 0.5 (19)	37.3 ± 0.5 (18)	37.6 ± 0.4 (15)	37.8 ± 0.4 (12)	37.8 ± 0.4 (12)	37.9 ± 0.4 (12)	37.9 ± 0.4 (12)	37.9 ± 0.4 (11)

Number of dogs indicated in brackets.

CMPS-SF, Glasgow Composite Measure Pain Scale score; DMED, dexmedetomidine; MOR, morphine; SED, sedation score; CRI, constant rate infusion; RT, rectal temperature; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; MAP, mean arterial blood pressure; CVP, central venous pressure; HR, heart rate.

[a]Significantly different from positive control group (MOR) at indicated time point ($p < 0.05$).

*Significant overall effect of treatment ($p = 0.0165$).

Table 7 Physiological parameters (mean ± SD) after initiation of rescue medication with MOR in combination with a CRI of DMED or MOR

		During rescue + CRI									
Variable	**Group**	**30 minutes**	**60 minutes**	**90 minutes**	**120 minutes**	**4 hours**	**8 hours**	**12 hours**	**16 hours**	**20 hours**	**24 hours**
HR (beats minute^{-1})	DMED*	78 ± 23 (11)	72 ± 25 (10)	81 ± 28 (10)	74 ± 30 (10)	78 ± 31 (10)	83 ± 35 (7)	81 ± 35 (7)	88 ± 32 (7)	79 ± 17 (5)	59 ± 30 (2)
	MOR	110 ± 22 (8)	102 ± 14 (5)	100 ± 15 (4)	89 ± 25 (4)	92 ± 18 (4)	91 ± 17 (3)	90 ± 18 (3)	100 ± 19 (3)	92 ± 28 (3)	89 ± 13 (3)
$_{f}$R (breaths minute^{-1})	DMED	27 ± 19 (9)	17 ± 8 (6)	21 ± 13 (8)	23 ± 18 (8)	16 ± 8 (8)	31 ± 18 (5)	25 ± 14 (7)	24 ± 11 (6)	22 ± 10 (5)	15 ± 13 (2)
	MOR	31 ± 21 (6)	33 ± 25 (4)	36 ± 28 (4)	38 ± 27 (4)	44 ± 18 (3)	43 ± 15 (3)	42 ± 26 (2)	31 ± 26 (2)	37 ± 18 (2)	32 ± 25 (3)
CVP (cmH_2O)	DMED	4.7 ± 2.5 (10)	3.8 ± 3.3 (10)	4.1 ± 2.9 (9)	3.5 ± 3.1 (10)	3.8 ± 3.3 (7)	3.4 ± 3.4 (7)	3.9 ± 2.6 (7)	3.6 ± 2.5 (7)	3.6 ± 1.8 (5)	4.3 ± 1.8 (2)
	MOR	2.3 ± 2.7 (8)	2.3 ± 2.8 (5)	3.0 ± 2.7 (4)	2.5 ± 2.5 (4)	3.4 ± 2.9 (4)	4.8 ± 3.9 (2)	4.3 ± 3.9 (2)	4.0 ± 2.0 (3)	4.2 ± 1.8 (3)	4.0 ± 2.3 (3)
MAP (mmHg)	DMED	108 ± 13 (10)	108 ± 14 (9)	112 ± 14 (9)	112 ± 19 (9)	104 ± 11 (9)	99 ± 12 (7)	100 ± 18 (7)	102 ± 11 (7)	109 ± 6 (5)	100 ± 16 (2)
	MOR	100 ± 20 (8)	102 ± 23 (5)	94 ± 13 (4)	99 ± 13 (4)	106 ± 7 (4)	116 ± 23 (3)	122 ± 11 (3)	112 ± 28 (3)	111 ± 26 (3)	124 ± 14 (3)
SAP (mmHg)	DMED	157 ± 22 (10)	162 ± 16 (9)	165 ± 14 (9)	161 ± 24 (9)	157 ± 18 (9)	146 ± 18 (7)	152 ± 23 (7)	152 ± 12 (7)	159 ± 8 (5)	151 ± 13 (2)
	MOR	159 ± 44 (8)	152 ± 46 (5)	149 ± 33 (4)	159 ± 37 (4)	167 ± 34 (4)	182 ± 51 (3)	181 ± 47 (3)	173 ± 46 (3)	173 ± 56 (3)	180 ± 32 (3)
DAP (mmHg)	DMED	88 ± 13 (10)	88 ± 12 (9)	91 ± 14 (9)	89 ± 16 (9)	83 ± 15 (9)	80 ± 12 (7)	79 ± 16 (7)	79 ± 9 (7)	90 ± 2 (5)	70 ± 0.0 (2)
	MOR	75 ± 16 (8)	80 ± 18 (5)	72 ± 7 (4)	78 ± 9 (4)	82 ± 4 (4)	90 ± 17 (3)	85 ± 14 (3)	89 ± 20 (3)	87 ± 20 (3)	87 ± 15 (3)

Number of dogs indicated in brackets.

CMPS-SF, Glasgow Composite Measure Pain Scale score; DMED, dexmedetomidine; MOR, morphine; SED, sedation score; CRI, constant rate infusion; RT, rectal temperature; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; MAP, mean arterial blood pressure; CVP, central venous pressure; HR, heart rate.

*Significant overall effect of treatment ($p = 0.0260$).

Table 8 Average incidence of cardiac rhythm abnormality (% of dogs) observed at baseline and during 24 hours CRI of DMED or MOR

			During CRI			
Arrhythmia	Group	Baseline −5 minutes	30 minutes	4 hours	12 hours	24 hours
1° AV block	DMED	11.8	25	20	20	11.1
	MOR	0	5	6.3	9.1	10
2° AV block	DMED	0	5	0	0	11.1
	MOR	5.3	5	6.3	9.1	20
Sinus arrhythmia	DMED	0	0	0	0	0
	MOR	5.3	5	6.3	9.1	30
Sinus pause	DMED	5.9	10	6.7	0	11.1
	MOR	0	10	6.3	18.2	0
Lengthened QT	DMED	17.6	55	40	10	22.2
	MOR	21.1	30	31.3	18.2	20
Sinus arrest	DMED	0	70	66.7	40	33.3
	MOR	5.3	5	6.3	9.1	30
SVPC	DMED	0	0	6.7	0	11.1
	MOR	0	10	0	0	0
VPC	DMED	5.9	10	6.7	20	11.1
	MOR	10.5	5	12.5	9.1	0

DMED, dexmedetomidine; MOR, morphine; CRI, constant rate infusion; SVPC, supraventricular premature complex; VPC, ventricular premature complex; AV, atrioventricular.

DMED bolus. HR was significantly lower in DMED dogs from T30 minutes to 4 hours. CVP was significantly higher in DMED dogs at T−5 and from T30–120 minutes. Arterial blood pressures were slightly higher in DMED dogs but only in DAP was the overall difference statistically significant (Table 6). Other differences in physiological parameters between dogs were already present before bolus administration of either MOR or DMED and were not attributed to the test drugs. After rescue medication HR was significantly lower in DMED group compared to MOR group at T30 and T60; f_R and SAP, MAP, DAP, CVP were similar between groups (Table 7).

Heart rhythm

A high incidence of benign ECG abnormalities (first degree AV block, second degree AV block, long QT interval) were observed in all dogs; the incidence of benign arrhythmias was not significantly different between groups (Table 8). Ventricular arrhythmias and a rapid idioventricular rhythm occurred in four dogs in the MOR group and two dogs in the DMED group. These arrhythmias were not treated and were not present throughout the entire study period. No adverse events arose from cardiac arrhythmias in either group.

Concomitant medication

A wide range of concomitant treatments were instituted peri-operatively with amoxicillin and clavulanic acid, metronidazole, metoclopramide, potassium supplementation, antacids, and furosemide, the most frequently used.

Of the medication groups that were discouraged from use only hydrocortisone (Solu-Cortef, 50 mg mL^{-1} (2 mL); Pfizer b.v., Capelle aan de IJssel, the Netherlands) was used in two cases of unilateral adrenalectomy for treatment of hyperadrenocorticism (one dog in the DMED group and one dog in the MOR group).

Fluid administration and urine production

The cumulative 24-hour amount of fluids given to DMED dogs [1.9 ± 1.2 L (n = 9)] was not significantly different from the amount given to MOR dogs [2.2 ± 0.8 L (n = 11)]. The cumulative 24-hour urine produced by DMED dogs [2.7 ± 1.4 L (n = 9)] was not significantly different from the amount produced by MOR dogs [2.1 ± 0.8 L (n = 11)].

Adverse events

Numerous adverse events were recorded during the study covering a wide range of conditions. The

incidence and severity of adverse events was not statistically different between groups. In four of 12 DMED dogs with at least one adverse event, these events were possibly or probably related to the pain control medication given (emesis, polyuria, and lethargy) and were considered to be of mild to moderate severity. Four adverse events (hypertension, hypovolaemia, oliguria and pneumonia) were deemed moderate in severity, but were considered unrelated to DMED administration.

In nine of 18 MOR dogs, with at least one adverse event, these events were possibly or probably related to the pain control medication given. All these events were considered mild in severity. Low urinary production (<1.5 mL kg^{-1} $hour^{-1}$) for different time points was recorded in six dogs. Hypertension, emesis and lethargy were the most frequent adverse events. Three adverse events (anaemia in two dogs and pneumonia) were deemed moderate in severity, but were considered unrelated to MOR administration.

Discussion

This is the first reported study to have evaluated the potential of a CRI DMED to provide postoperative pain management in dogs requiring intensive analgesia therapy. The results from this study demonstrated that the DMED CRI contributed to a stable plane of post-operative analgesia for up to 24 hours in critically ill patients. Dogs that did not require rescue medication received DMED as a sole analgesic and appeared to be comfortable, quiet and relaxed. Although there were no differences in pain score between groups in the first study period, DMED provided better analgesia than MOR during the 12 to 24-hour time period. However it should be considered that in the later study period, dogs that were deemed painful (score ≥5) had been removed from the analysis to the *post-rescue* protocol and pain scores in both the MOR and DMED group were very low.

Estimating pain severity in individual animals can be difficult as pain intensity may be unrelated to the underlying disease (Hansen 2005) and every animal responds to pain differently. It is particularly difficult in critically ill dogs because systemic disease may obtund normal behavioural signs of pain. This study highlighted two important aspects of pain management in critically ill animals; the importance of regular pain assessment using a validated pain score system and the need to tailor analgesia to the individual. The CMPS-SF is the only pain scale that has been validated for the assessment of acute pain in dogs (Holton et al. 2001; Morton et al. 2005; Murrell et al. 2008). Use of the CMPS-SF has been validated at the University Utrecht and it was shown to be a reliable clinical tool to define different pain intensities and change in pain score over time in a population of dogs undergoing a variety of surgical procedures (Murrell et al. 2008). Use of a single investigator also limited the variability in assessing pain using the CMPS-SF.

Although the use of a DMED CRI for postoperative pain management has not been previously studied in dogs, results from three studies in dogs evaluating the use of DMED as a sedative and anaesthetic adjunct served as supportive evidence for choosing the DMED dose evaluated in the present study (Pascoe et al. 2005; Lin et al. 2008; Uilenreef et al. 2008). The DMED dose was calculated based on body surface area rather than body weight because dosing of alpha-2 agonists based on body weight has been associated with different levels of sedation between groups of dogs (Vaha-Vahe 1989). The dose scheme in the present study was identical to the dose scheme used in another study (Lin et al. 2008) where the plasma concentration of DMED was shown to be stable over 24 hours. The dose of MOR CRI used in the present study was the standard dose used at the ICU of the DCSCA for postoperative pain management in dogs following invasive surgery. This dose is also reported to be widely used clinically for postoperative pain management in different institutions. Lucas et al. (2001) showed that administration of MOR CRI at a dose of 0.12 mg kg^{-1} $hour^{-1}$ provided analgesia in dogs undergoing laparotomy. However, in more recent studies (Kukanich et al. 2005a,b), published after the start of the present investigation, a higher dose of MOR than the dose rate used in the present study was required to maintain analgesia in a mechanical analgesiometry model. In the light of these recent findings (Kukanich et al. 2005a,b) it is possible that the dose of MOR used here was insufficient to achieve adequate analgesia at all times. An underlying assumption of the study design was that the doses of MOR and DMED chosen were bio-equivalent in terms of analgesia. Unfortunately, the bio-equivalent doses of MOR and DMED for analgesia have not been evaluated. It is possible that different results would have been obtained if different doses of test drugs had been evaluated.

Dexmedetomidine-induced sedation is mediated through an effect at α_2 receptors located in the locus coeruleus, which controls vigilance and modulates sympathetic outflow (Correa-Sales et al. 1992; Nelson et al. 2003). DMED caused greater sedation than MOR in the first 1.5 hours of the study, which may be attributed to the rapid increase in plasma concentration following the DMED loading dose and start of the CRI. However, the greater sedation achieved with DMED was not judged to impair pain scoring or have a negative effect on postoperative recovery. The sedative effect of DMED also seemed to decrease over time. Dogs receiving DMED appeared quiet and relaxed throughout the study, but easily rousable when interaction was required. This effect has also been described in humans where the sedative effect of DMED has been described as 'arousable or co-operative sedation' (Hall et al. 2000; Nelson et al. 2003; Gerlach & Dasta 2007). In this study, most of the animals receiving DMED were observed to be calmer than the MOR dogs. Stress and anxiety can be considered as an important negative part of hospitalization, contributing in an unconstructive way to the overall pain experience and negatively influencing recovery (Hansen 2005). Sedation should not be considered as a substitute for analgesia but it has an important role in patients that show behavioural manifestation of distress such that it limits their ability to eat, sleep and rest. DMED CRI seems able to provide minimal sedation and good anxiolysis in dogs in the postoperative setting.

A major concern related to the use of alpha-2 agonists in dogs is the effects of these drugs on the cardiovascular system. In this study, all the expected cardiovascular changes of a DMED CRI were observed. However, none of these caused clinically significant effects. The incidence of bradyarrhythmia, sinus pause and different types of heart block varies inversely with mean HR in healthy conscious dogs and during the peri-anaesthetic period in dogs premedicated with DMED (Ulloa et al. 1995; Kuusela et al. 2002; Lin et al. 2008). These types of arrhythmias have been attributed to a decreased sympathetic and increased vagal tone induced by alpha-2 agonists and are not considered life-threatening (Sinclair 2003). There was a higher incidence of ECG abnormalities in the present study compared to previous studies in healthy animals (Ulloa et al. 1995; Kuusela et al. 2002; Lin et al. 2008). However, the incidence of arrhythmias was not significantly different between the two treatment groups and may be attributed to underlying disease processes. It has been reported that dogs undergoing splenectomy or surgery for gastric dilation and volvulus (GDV) have a higher incidence of ventricular and supraventricular arrhythmias (Marino et al. 1994; Miller et al. 2000) than other dogs. In the six dogs in which serious arrhythmias were recorded, two of them were operated on for a GDV, three underwent splenectomy and one dog had a uroabdomen. The cardiac arrhythmias in the MOR group could also be attributed to myocardial stimulation by high concentrations of circulating epinephrine as a result of histamine-stimulated adrenal secretion (Muldoon et al. 1987; Guedes et al. 2006).

Approximately half of the dogs in both groups required rescue medication. This was not unexpected given the population. In anticipation that some animals may be painful on monotherapy we designed the study so that we had a *post-rescue* protocol to which we could allocate dogs that required rescue medication during the 24 hours of the study. A clinically relevant and unexpected result of this study arose following analysis of the data from the animals that received rescue medication. In these dogs, there were few significant differences with respect to cardiovascular parameters and sedation between the two groups, while the CMPS-SF score was significantly lower for DMED dogs receiving rescue MOR compared to MOR dogs receiving rescue MOR administration. The close association between opioid and alpha$_2$-adrenergic receptors and their enhanced antinociceptive actions following simultaneous administration of opioids and alpha-2 agonists at the sympathetic nerve endings in the spinal cord is well recognized (Ossipov et al. 1990; Shelly 2001; Fairbanks et al. 2002). The results of our investigation substantiate this improved analgesia when DMED and MOR are combined, and support the use of multi-modal analgesic techniques.

There are a number of limitations to this complex study that should be considered during interpretation of the data. Although no statistical differences were highlighted between the two groups of patients in regards to their age, body weight, type of surgery and length of surgery, dogs were referred to the hospital with different medical and surgical conditions, different clinical statuses and different responses to handling and caging. In conclusion, variability in a clinical population is unavoidable. The variability in underlying illness may have

confounded the pain scoring in the present study, particularly because different surgical procedures may result in different degrees of postoperative pain. On the other hand, studying a diverse clinical population could be considered advantageous because the investigation has been able to show the clinical reality of an analgesic strategy in a heterogeneous group of patients recovering from invasive surgery in an ICU setting. The use of an accepted acute pain scoring system (CMPS-SF) by a well-trained single investigator throughout the study served to minimise the effect of variation associated with the clinical setting. A power analysis was carried out before the start of the study based on the assumption that a numerical difference in pain score of 3 using the CMPS-SF would be clinically relevant when comparing post-operative analgesia using MOR of DMED CRI. These values were derived from a multi-centre study evaluating the CMPS-SF in a clinical setting (Reid et al. 2007), which found that the 95% confidence interval for the difference in median pain score (dogs requiring analgesia-no analgesia) was (3–5). That study also defined an analgesic intervention level of 5/20 and higher, which was adopted in the present investigation. Mean pain scores were low (around 2–3) in dogs that did not require rescue analgesia, which may have limited the ability of the study to identify differences between groups. However, there was also no significant difference between the number of animals in each treatment group requiring rescue analgesia, which supports the conclusion that MOR and DMED CRI at the doses tested were equi-analgesic.

This study has evaluated and shown the potential of a CRI DMED to contribute to a balanced and stable plane of postoperative analgesia for up to 24 hours in a critically ill patient population. The DMED CRI regimen was also shown to be tolerated well clinically, even in a population of dogs classified as ASA status 3 or 4 before surgery. Rescue analgesia was required in both MOR and DMED groups suggesting that the doses tested in this study were not appropriate to achieve an adequate level of analgesia in the entire study population. Different analgesic effects and levels achieved by using different CRI DMED doses have not yet been quantified in a clinical model. It is possible that some animals that remained painful on the monotherapy used in this study would have benefited from the administration of a higher dose of MOR or DMED to attain an adequate analgesia level.

Although DMED is unlikely to become a first line analgesic drug for use in all animals after surgery our findings indicate that DMED should be considered a well tolerated and reliable analgesic drug when given by continuous rate infusion. It is likely to be particularly valuable as part of a multi-modal analgesia protocol and as an adjunct to opioid analgesia in dogs where effective pain management is required.

Acknowledgements

We thank Orion Pharma (Turku, Finland) for their generous donation of DMED hydrochloride and MOR hydrochloride, and for performing the statistical analyses. We acknowledge the support of the staff of the Division of Anaesthesiology and Intensive Care of the Faculty of Veterinary Medicine, Utrecht University, Utrecht, the Netherlands. Dr Sietske Mesu is thanked for her assistance in preparing the CRI infusions; Dr Tom Mullany is thanked for his expert analysis of the electrocardiograms.

Financial support

The study was funded by Orion Corporation, Orion Pharma Animal Health, PO Box 425, 20101 Turku, Finland.

References

Arain SR, Ruehlow RM, Uhrich TD et al. (2004) The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg 98, 153–158.

Barnhart M, Hubbel JAE, Muir WW (2000) Evaluation of the analgesic properties of acepromazine maleate, oxymorphone, medetomidine and a combination of acepromazine-oxymorphone. Vet Anaesth Analg 27, 89–96.

Bloor BC, Frankland M, Alper G et al. (1992) Hemodynamic and sedative effects of dexmedetomidine in dog. J Pharmacol Exp Ther 263, 690–697.

Correa-Sales C, Rabin BC, Maze M (1992) A hypnotic response to dexmedetomidine, an $\alpha 2$ agonist, is mediated in the locus coeruleus in rats. Anesthesiology 76, 948–952.

Cullen LK (1996) Medetomidine sedation in dogs and cats: a review of its pharmacology, antagonism and dose. Br Vet J 152, 519–535.

Ebert TJ, Hall JE, Barney JA et al. (2000) The effect of increasing plasma concentration of dexmedetomidine in humans. Anesthesiology 93, 382–394.

Fairbanks CA, Stone LS, Kitto KF et al. (2002) α_2-Adrenergic receptors mediated spinal analgesia and adrenergic opioid synergy. J Pharm Exp Ther 300, 282–290.

Gerlach AT, Dasta JD (2007) Dexmedetomdine: an updated review. Ann Pharmacother 41, 245–254.

Granholm MM, McKusick BC, Westerholm FC et al. (2007) Evaluation of the clinical efficacy and safety of intramuscular and intravenous dexmedetomidine or medetomidine in dogs and their reversal with atipamezole. Vet Rec 160, 891–897.

Grimm KA, Tranquilli W, Thurmon J et al. (2000) Duration of nonresponse to noxious stimulation after intramuscular administration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. Am J Vet Res 61, 42–47.

Guedes AGP, Rude EP, Rider MA (2006) Evaluation of histamine release during constant rate infusion of morphine in dogs. Vet Anaesth Analg 33, 28–35.

Guedes AGP, Papich MG, Rude EP et al. (2007) Pharmacokinetics and physiological effects of two intravenous infusion rates of morphine in conscious dogs. J Vet Pharmacol Ther 30, 224–233.

Hall JE, Uhrich TD, Barney JA et al. (2000) Sedative, amnestic and analgesic properties of small-dose dexmedetomidine infusion. Anesth Analg 90, 699–705.

Hansen BD (2005) Analgesia and sedation in the critical ill. J Vet Emerg Crit Care 15, 285–294.

Hofmeister EH, Herrington J, Mazzaferro EM (2006) Opioid dysphoria in three dogs. J Vet Emerg Crit Care 16, 44–49.

Holton L, Reid J, Scott M (2001) Development of a behaviour-based scale to measure acute pain in dogs. Vet Rec 28, 148 525–531.

Jin F, Chung F (2001) Multimodal analgesia for postoperative pain control. J Clin Anesth 13, 524–539.

Kukanich B, Lascelles BD, Papich MG (2005a) Use of a Von Frey device for evaluation of pharmacokinetics and pharmacodynamics of morphine after intravenous administration as an infusion or multiple doses in dogs. Am J Vet Res 66, 1968–1974.

Kukanich B, Lascelles BD, Papich MG (2005b) Pharmacokinetics of morphine and plasma concentration of morphine-6-glucuronide following morphine administration in dogs. J Vet Pharmacol Ther 28, 371–376.

Kuusela E, Raekallio M, Anttila M et al. (2000) Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Ther 23, 15–20.

Kuusela E, Raekallio M, Vaisanen M et al. (2001a) Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. Am J Vet Res 62, 1073–1080.

Kuusela E, Vainio O, Kaistinen A et al. (2001b) Sedative, analgesic, and cardiovascular effects of levomedetomidine alone and in combination with dexmedetomidine in dogs. Am J Vet Res 62, 616–621.

Kuusela E, Raekallio M, Hietanen H et al. (2002) 24-hour Holter-monitoring in the perianaesthetic period in dogs premedicated with dexmedetomidine. Vet J 164, 235–239.

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

Lucas AN, Firth AM, Anderson GA et al. (2001) Comparison of the effects of morphine administered by constant rate infusion or intermittent intramuscular injection in dogs. J Am Vet Med Assoc 218, 884–891.

Marino DJ, Matthiesen DT, Fox PR et al. (1994) Ventricular arrhythmias in dogs undergoing splenectomy: a prospective study. Vet Surg 23, 101–106.

Miller TL, Schwartz DS, Nakayama T et al. (2000) Effect of acute gastric distension and recovery on tendency for ventricular arrhythmias in dogs. J Vet Int Med 14, 436–444.

Morton CM, Reid J, Scott EM et al. (2005) Application of a scaling model to establish and validate an interval level pain scale for assessment of acute pain in dogs. Am J Vet Res 66, 2154–2166.

Muir WW, Woolf CJ (2001) Mechanism of pain and their therapeutic implications. J Am Vet Med Assoc 219, 1346–1356.

Muldoon SM, Freas W, Mahla ME et al. (1987) Plasma histamine and catecholamine levels during hypotension induced by morphine and compound 48/80. J Cardiovasc Pharmacol 9, 578–583.

Murrell JC, Psatha EP, Scott EM et al. (2008) Application of a modified form of the Glasgow pain scale in a veterinary teaching centre in the Netherlands. Vet Rec 162, 403–408.

Nelson LE, Lu J, Guo T et al. (2003) The α_2–adrenoceptors agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 98, 428–436.

Ossipov MH, Harris S, Lloyd P et al. (1990) Antinoceptive interaction between opioids and medetomidine: systemic additivity and spinal synergy. Anesthesiology 73, 1227–1235.

Pascoe PJ, Raekallio M, Kuusela E et al. (2005) Changes in the minimum alveolar concentration of isoflurane and some cardiopulmonary measurements during three continuous infusion rates of dexmedetomidine in dogs. Vet Anaesth Analg 33, 97–103.

Reid J, Nolan AM, Hughes JML et al. (2007) Development of the short-form Glasgow Composite Measure Pain Scale (CMPS-SF) and derivation of an analgesic intervention score. Anim Welf 16, 97–104.

Shehabi Y, Ruettimann U, Adamson H et al. (2004) Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. Int Care Med 30, 2188–2196.

Shelly MP (2001) Dexmedetomidine: a real innovation or more of the same. Br J Anaesth 87, 678–679.

Sinclair MD (2003) A review of the physiological effects of alpha2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J 44, 885–897.

Tobias JD, Berkenbosch JW (2004) Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 97, 451–455.

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

Ulloa HM, Houston BJ, Altrogge DM (1995) Arrhythmia prevalence during ambulatory electrocardiographic monitoring of beagles. Am J Vet Res 56, 275–281.

Unlugenc H, Gunduz M, Guler T et al. (2005) The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. Eur J Anaesth 22, 386–391.

Urquhart J (2000) Controlled drug delivery: therapeutic and pharmacological aspects. J Intern Med 248, 357–376.

Vaha-Vahe T (1989) Clinical evaluation of medetomidine, a novel sedative and analgesic drug for dogs and cats. Acta Vet Scand 30, 267–273.

Vainio O, Vaha-Vahe T, Palmu L (1989) Sedative and analgesic effects of medetomidine in the dog. J Vet Pharmacol Ther 12, 225–231.

Venn RM, Grounds RM (2001) Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patients and clinician perceptions. Br J Anaesth 87, 684–690.

Venn RM, Bradshaw CJ, Spencer R et al. (1999) Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit. Anaesthesia 54, 1136–1142.

Received 29 September 2008; accepted 20 October 2008.