Cardiopulmonary and sedative effects of the peripheral α_2-adrenoceptor antagonist MK 0467 administered intravenously or intramuscularly concurrently with medetomidine in dogs

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Objective—To evaluate the cardiopulmonary and sedative effects of the peripheral α_2-adrenoceptor antagonist MK 0467 when administered IM or IV concurrently with medetomidine in dogs.

Animals—8 adult dogs.

Procedures—Dogs received 20 µg of medetomidine/kg, IM, alone or concurrently with MK 0467 (0.4 mg/kg, IM), and 10 µg of medetomidine/kg, IV, alone or concurrently with MK 0467 (0.2 mg/kg, IV), in a randomized crossover study. Sedation characteristics were scored and hemodynamic measurements and arterial and mixed-venous blood samples for blood gas analysis were obtained before (time 0; baseline) and for 90 minutes after treatment.

Results—Heart rate (HR), mixed-venous partial pressure of oxygen ($P\bar{v}O_2$), and cardiac index (CI) were significantly lower and mean arterial blood pressure (MAP), systemic vascular resistance (SVR), and oxygen extraction ratio (ER) were significantly higher after administration of medetomidine IM or IV, compared with baseline values. Administration of medetomidine and MK 0467 IM caused a significantly higher heart rate, CI, and $P\bar{v}O_2$ and significantly lower MAP, SVR, and ER for 60 to 90 minutes than did IM administration of medetomidine alone. Administration of medetomidine and MK 0467 IV caused a significantly higher CI and $P\bar{v}O_2$ and significantly lower MAP, SVR, and ER for 45 to 90 minutes than did IV administration of medetomidine alone. There was no significant difference in sedation scores among treatments.

Conclusions and Clinical Relevance—In dogs, MK 0467 administered concurrently with medetomidine IV or IM reduced the cardiovascular effects of medetomidine but had no detectable effect on sedation scores. (*Am J Vet Res* 2012;73:587–594)

Medetomidine, an α_2-adrenoceptor agonist, is a popular sedative and preanesthetic agent for use in dogs because of the consistent, reliable, predictable, and dose-dependent CNS depression associated with both IV and IM administration. Unfortunately, use of medetomidine and other α_2-adrenoceptor agonists in dogs is associated with pronounced adverse cardiovascular effects. Specifically, these agents cause marked peripheral vasoconstriction, dramatic increases in arterial blood pressure, and decreases in HR and CO.[1–4] Although there are no clinically important changes in arterial oxygenation when α_2-adrenoceptor agonists are administered alone to dogs, the combination of a reduction in D_{O_2} that is out of proportion to the decrease in $\dot{V}O_2$ leads to an increase in ER and a decrease in $P\bar{v}O_2$, even in healthy dogs receiving low to moderate doses of α_2-adrenoceptor agonists.[4]

Abbreviations

Ca_{O_2}	Arterial oxygen content
CI	Cardiac index
CO	Cardiac output
$C\bar{v}_{O_2}$	Mixed-venous oxygen content
CVP	Central venous pressure
DAP	Diastolic arterial blood pressure
D_{O_2}	Oxygen delivery
ER	Oxygen extraction ratio
HR	Heart rate
MAP	Mean arterial blood pressure
MPAP	Mean pulmonary artery pressure
PAOP	Pulmonary artery occlusion pressure
$P\bar{v}_{O_2}$	Mixed-venous partial pressure of oxygen
RR	Respiratory rate
Sa_{O_2}	Arterial oxygen saturation
SAP	Systolic arterial blood pressure
SV	Stroke volume
$S\bar{v}_{O_2}$	Mixed-venous oxygen saturation
SVR	Systemic vascular resistance
$\dot{V}_{O_2}$	Oxygen consumption

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Investigators have used several approaches to prevent or ameliorate the unwanted cardiovascular effects of α_2-adrenoceptor agonists. To counter the reduction in HR, CO, and D_{O_2} associated with α_2-adrenoceptor agonist administration, anticholinergic administration prior to, or concurrent with, α_2-adrenoceptor agonists has been evaluated in dogs.[5–7] In addition to an increase in arrhythmias associated with concurrent atropine and α_2-agonist administration, several studies[3,6] have found a marked increase in systemic arterial blood pressures associated with the increase in HR. Investigators in 1 study[6] found that glycopyrrolate prevented bradycardia associated with romifidine in dogs; however, it exacerbated the increase in systemic arterial blood pressures. Another study[7] found that glycopyrrolate given with romifidine increased echocardiographic indices of myocardial workload and decreased measures of myocardial contractility, compared with results for dogs receiving romifidine alone. Others have found similar results in dogs administered glycopyrrolate or atropine prior to or in combination with medetomidine.[4,8] Although anticholinergic use may be lifesaving when bradycardia is profound, indiscriminate use of anticholinergics with α_2-agonist adrenoceptor agonists can cause hypertension, cardiac arrhythmias, and increased cardiac work and routine use is currently not recommended.[5–9]

Because most sedative and anesthetic agents induce a dose-dependent effect on the cardiovascular system, another approach for minimizing the adverse effects of α_2-adrenoceptor agonists has been to use doses lower than initially recommended but that will still induce clinically reliable sedation. Unfortunately, evaluation of medetomidine's cardiovascular effects in dogs over a range of doses has revealed that IV administration at doses as low as 1 μg/kg causes significant alterations in cardiovascular function, with a ceiling effect for the magnitude (but not the duration) at a dose of 5 μg/kg.[1] Because consistent sedation is unreliable at doses ≤ 5 μg/kg, the use of dose reduction of medetomidine as a method to avoid cardiovascular effects is not clinically feasible.[10]

In contrast to the desirable centrally mediated sedative effects of α_2-adrenoceptor agonists, the cardiovascular effects of these agents are largely the result of activation of α_2-adrenoceptors located on the peripheral vasculature. The peripheral α_2-adrenoceptor antagonist L-659,066 (now known as MK 0467), when administered IV before dexmedetomidine or medetomidine administration, minimizes bradycardia, hypertension, and increases in SVR associated with these drugs in dogs.[4,11] In a more recent study[12] in dogs, investigators found that simultaneous IV administration of dexmedetomidine and MK 0467 minimized the bradycardia, hypertension, and reduction in CO associated with dexmedetomidine. However, to our knowledge, no studies have been conducted to evaluate the effects of concurrent administration of α_2-adrenoceptor agonists and MK 0467 on variables (eg, ER and $P\bar{v}O_2$) that reflect the adequacy of oxygen supply versus global tissue demand. In addition, considering that α_2-adrenoceptor agonists are administered IV and IM in clinical practice, ideally MK 0467 would be effective when administered concurrently with the α_2-adrenoceptor agonists IM as well as IV. To our knowledge, concurrent administration of MK 0467 and an α_2-adrenoceptor agonist via the IM route has not been reported in dogs.

The purpose of the study reported here was to evaluate the effects of the receptor antagonist MK 0467 when administered IV and IM at the same time as medetomidine. We hypothesized that MK 0467, when administered concurrently with medetomidine, would prevent the α_2-receptor–induced increase in systemic arterial blood pressures, SVR, and ER and the decrease in $P\bar{v}O_2$. We also evaluated whether there was any detectable effect of the receptor antagonist on the sedation induced by medetomidine.

Materials and Methods

Animals—Eight healthy adult male mixed-breed dogs with a mean ± SD body weight of 27.7 ± 3.2 kg were used in the study. Dogs were assessed as healthy on the basis of results of physical examination, a CBC, and serum biochemical analysis.[a] Food but not water was withheld from the dogs beginning 12 hours prior to the start of the study. The experimental protocol was reviewed and approved by the Animal Care Committee of the University of Guelph.

Treatment groups—Dogs were randomly assigned to 4 groups. Dogs received each of 4 treatments in accordance with a Latin square design; there was a minimum of 7 days between subsequent treatments. Treatments consisted of IM administration of 20 μg of medetomidine[b]/kg alone, IM administration of that dose of medetomidine concurrently with administration of 0.4 mg of MK 0467[c]/kg, IV administration of 10 μg of medetomidine/kg alone, and IV administration of that dose of medetomidine concurrently with 0.2 mg of MK 0467/kg. Medetomidine was administered first and was immediately followed by administration of MK 0467 or an equal volume of saline (0.9% NaCl) solution. Intramuscular injections were administered in the lumbar musculature, and IV injections were administered via a catheter inserted into a cephalic vein.

Drug preparation—At the beginning of each experimental period, the powder form of MK 0467 was mixed with sterile saline solution to create a 5 mg/mL solution. For IM treatments, the calculated medetomidine and medetomidine-receptor antagonist doses were each combined with sterile saline solution to create a standard 2-mL volume for administration.

Instrumentation—Dogs were anesthetized, and instrumentation was performed as described elsewhere.[4] In brief, a 20-gauge, 4.8-cm catheter was inserted into a cephalic vein of each dog, and anesthesia was induced by IV administration of a 1% propofol solution.[d] Dogs were orotracheally intubated with an appropriately sized, cuffed endotracheal tube connected to a universal F-circuit attached to an anesthetic machine. Anesthesia was maintained with isoflurane[e] delivered in oxygen, with a flow rate of 60 to 100 mL/kg/min and the vaporizer adjusted to maintain a light surgical plane of anesthesia.

Each dog was positioned in lateral recumbency, and a second 20-gauge, 4.8-cm catheter was placed in

a dorsal pedal artery for direct measurement of SAP, MAP, and DAP and for collection of blood samples for blood gas analysis. Hair over a jugular groove was clipped and the skin surgically prepared. The subcutaneous tissue was infiltrated with 0.5 mL of 2% lidocaine hydrochloride,[f] and an 8.5F introducer[g] was placed in that jugular vein. A 7F thermodilution catheter[h] was placed via the introducer and advanced into the pulmonary artery by use of fluoroscopic guidance. The distal port of the thermodilution catheter was used for collection of mixed-venous blood samples and measurement of core body temperature, PAOP, and MPAP. The proximal port of the thermodilution catheter was used for measurement of CVP and injection of cold injectate (5% dextrose solution[i]) to measure CO. All pressure transducers[j] were calibrated by use of a mercury manometer before each experimental period.

Procedures—Each catheter site was bandaged after insertion of a catheter. After instrumentation and catheter bandaging were completed, isoflurane administration was discontinued and the dogs were allowed to recover from anesthesia. Each experimental period began once the dogs could stand and walk without ataxia but a minimum of 30 minutes after extubation and a minimum of 60 minutes after propofol administration. At the start of each experimental period, an observer who was unaware of the treatments assigned for each dog assessed sedation. Sedation was scored in accordance with a 5-point sedation index adapted from another study[13] (**Appendix**). In brief, the sedation assessment consisted of rating the posture, palpebral reflex, eye position, jaw tone, response to tongue manipulation, and response to noise (maximum possible sedation score, 19). Dogs were then gently restrained in the standing position, and baseline cardiopulmonary variables (RR, HR, SAP, DAP, MAP, MPAP, PAOP, CVP, and CO) and body temperature measurements were recorded. The zero reference point for pressure measurements[j] was the point of the shoulder when dogs were standing and the manubrium when dogs were in lateral recumbency. Arterial and mixed-venous blood samples were collected simultaneously, and P_{O_2}, P_{CO_2}, hemoglobin concentration, hemoglobin saturation, and pH were measured by use of a blood gas analyzer[k] within 5 minutes after sample collection. Temperature-corrected values were recorded. Bicarbonate and base excess values were calculated.[k] The CO was measured by use of a CO computer[l] via the thermodilution technique, with an injectate of 10 mL of cold 5% dextrose solution. At each time point, CO was recorded as the mean of at least 3 values with a variation of ≤ 10%.

After recording baseline values and collecting blood samples (time 0), the drug treatments were administered. Five minutes after administration of the assigned treatment, dogs were placed in lateral recumbency. Sedation scoring, recording of cardiopulmonary variables and body temperature, and measurement of CO was performed, and blood samples were collected for analysis. All data and sample collection was repeated 15, 30, 45, 60, 75, and 90 minutes after drug administration. The CI, SV, SVR, Ca_{O_2}, $C\bar{v}_{O_2}$, D_{O_2}, $\bar{V}_{O_2}$, and ER were calculated by use of standard equations.[14] At the end of each experimental period, meloxicam[m] (0.1 mg/kg) was administered IV to all dogs and catheters were removed.

Statistical analysis—Statistical analyses were performed by use of commercially available software.[n] Data were reported as mean ± SD. The Shapiro-Wilk test was used to evaluate normality of the data distribution. Cardiovascular data were analyzed via an ANOVA for repeated measures. The sedation scores did not yield continuous data and were not expected to be normally distributed. A nonparametric test is indicated for this type of data; however, no nonparametric test was appropriate for the design of the study. Given that the sedation scores were normally distributed (on the basis of results for the Shapiro-Wilk test), the sedation data were also analyzed by use of an ANOVA for repeated measures. Treatment, time, and treatment-by-time interactions were included in the tests. When significant differences were detected or there was an overall effect of time, a post hoc Dunnett test was used to compare treatment values with baseline values. Group means were compared by use of the Tukey test. Values of $P < 0.05$ were considered significant.

Results

All dogs were profoundly sedated after drug administration, and there were no significant differences in sedation scores among treatments at any time point. For each treatment, the sedation score was significantly higher than the baseline value at every time point after drug administration (**Figure 1**).

We did not detect differences among treatments at baseline for any of the cardiopulmonary variables, ex-

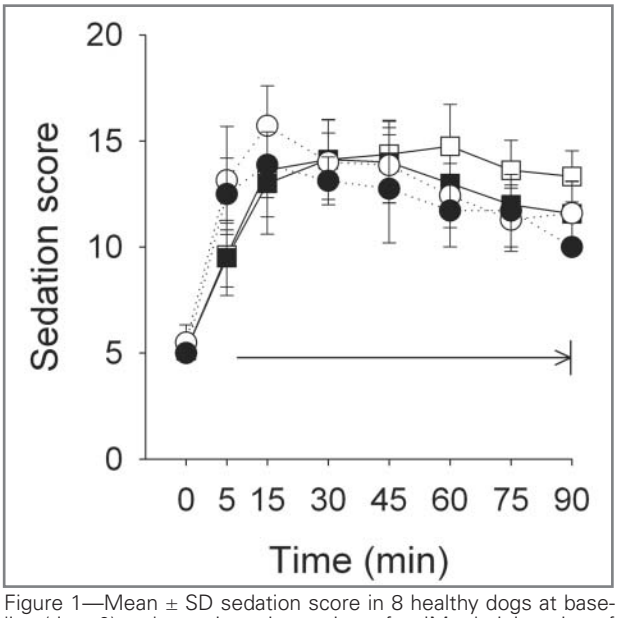

Figure 1—Mean ± SD sedation score in 8 healthy dogs at baseline (time 0) and at various time points after IM administration of medetomidine (20 µg/kg; white squares), concurrent IM administration of that dose of medetomidine and MK 0467 IM (0.4 mg/kg; black squares), IV administration of medetomidine (10 µg of medetomidine/kg; white circles), and concurrent IV administration of that dose of medetomidine and MK 0467 (0.2 mg/kg; black circles). Maximum possible sedation score was 19. For all treatments, values for all time points indicated by the arrow differed significantly ($P < 0.05$) from the value at baseline.

cept for SV, for which there was a significant difference between IM treatments at baseline. Five minutes after IV or IM administration of medetomidine, HR, SV, CI, CO, RR, $S\bar{v}O_2$, $P\bar{v}O_2$, $C\bar{v}O_2$, DO_2, $\dot{V}O_2$, and body temperature were significantly lower than baseline values (**Figures 2 and 3**; **Tables 1–3**). These variables remained significantly below baseline values for the entire 90 minutes of the study, except for $C\bar{v}O_2$ when dogs received IV administration of medetomidine alone, which returned to values not significantly different from the baseline value at 90 minutes. Values for SAP, MAP, DAP, MPAP, CVP, PAOP, SVR, arterial and mixed-venous hemoglobin concentrations, CaO_2, and ER were significantly higher after IM or IV administration of medetomidine, compared with baseline values. When dogs received IM administration of medetomidine alone, these variables remained above baseline values for the duration of the experimental period, whereas when dogs received IV administration of medetomidine alone, most variables remained significantly different from baseline values, except for SAP (which returned to values not significantly different from baseline values by 60 minutes) and MAP and DAP (which returned to values not significantly different from baseline values by 75 minutes).

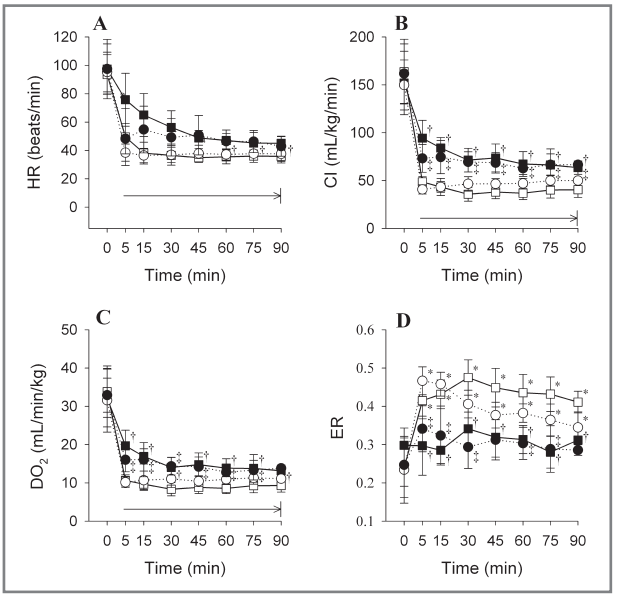

Figure 2—Mean ± SD values for the cardiovascular variables HR (A), CI (B), DO_2 (C), and ER (D) in the same 8 healthy dogs as in Figure 1. For all treatments, values for all time points indicated by the arrow differed significantly ($P < 0.05$) from the value at baseline. *Within a treatment, value differs significantly ($P < 0.05$) from the value at baseline. †Within a time point, values differ significantly ($P < 0.05$) from the value for the medetomidine IM treatment. ‡Within a time point, value differs significantly ($P < 0.05$) from the value for the medetomidine IV treatment. *See* Figure 1 for remainder of key.

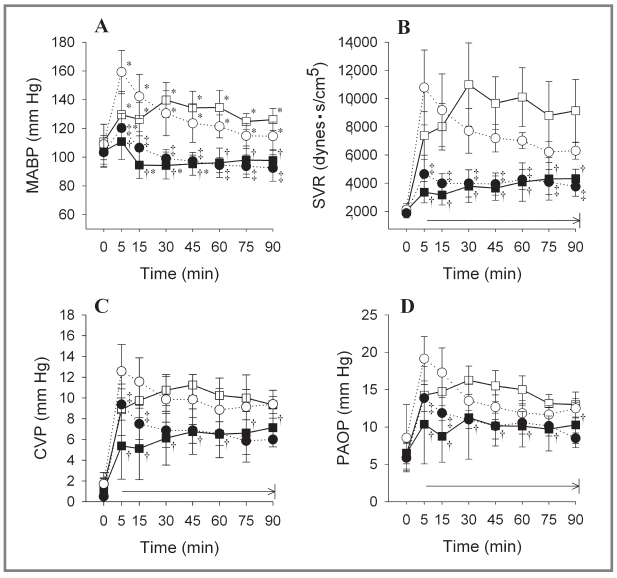

Figure 3—Mean ± SD values for the cardiovascular variables MAP (A), SVR (B), CVP (C), and PAOP (D) in the same 8 healthy dogs as in Figure 1. *See* Figures 1 and 2 for remainder of key.

In contrast to administration of medetomidine alone, there were no significant differences relative to baseline values throughout the experimental period for MAP, PAOP, and ER for both treatments involving administration of medetomidine and MK 0467. For IM administration of medetomidine and MK 0467, $P\bar{v}O_2$ was not significantly different from baseline values at any subsequent time point, whereas for IV administration of medetomidine and MK 0467, $P\bar{v}O_2$ was significantly different from baseline values from 5 to 90 minutes after administration. Similar to administration of medetomidine alone, HR, CI, CO, RR, DO_2, and $\dot{V}O_2$ were significantly lower and SVR, CVP, and PAOP were significantly higher at 5 to 90 minutes, compared with baseline values, for IM and IV administration of medetomidine and MK 0467. The PaO_2 was also significantly lower than baseline values at several time points after administration of medetomidine and MK 0467, although mean PaO_2 did not decrease below 83.5 mm Hg for any treatment throughout the study. The lowest PaO_2 was 71.4 mm Hg in a dog after IM administration of medetomidine alone. The lowest PaO_2 in a dog for the other treatments was 72.3 mm Hg after IM administration of medetomidine and MK 0467, 62.2 mm Hg after IV administration of medetomidine alone, and 74.6 mm Hg after IV administration of medetomidine and MK 0467.

Concurrent IM administration of the receptor antagonist MK 0467 and medetomidine resulted in a significantly higher HR, CO, CI, DO_2, $S\bar{v}O_2$, and $P\bar{v}O_2$ and a significantly lower MAP, DAP, CVP, PAOP, and SVR, compared with values after IM administration of medetomidine alone, beginning 5 minutes after drug administration and continuing until the end of the experimental period. The SAP, MPAP, CaO_2, and arterial and mixed-venous hemoglobin concentrations were significantly lower after IM administration of medetomidine and MK 0467, compared with values after IM administration of medetomidine alone, beginning 15 minutes after drug administration and continuing until the end of the experimental period. Arterial pH and $PaCO_2$ were significantly higher after IM administration of medetomidine and MK 0467, compared with values after IM administration of medetomidine alone, from 5 to 75 minutes, and SaO_2 was significantly higher after IM administration of medetomidine and MK 0467, compared with values after IM administration of medetomidine alone, only at 45 minutes after drug administration.

Overall, concurrent IV administration of MK 0467 and medetomidine resulted in differences relative to IV administration of medetomidine alone that were similar to those detected when comparing the 2 IM treat-

Table 1—Mean ± SD values for cardiovascular variables in 8 healthy dogs at baseline (time 0) and at various time points after IM administration of medetomidine (20 μg/kg), concurrent IM administration of that dose of medetomidine and MK 0467 (0.4 μg/kg; combination), IV administration of medetomidine (10 μg/kg), and concurrent IV administration of that dose of medetomidine and MK 0467 (0.2 μg/kg; combination).

Variable	Treatment	Route of administration	Time after administration (min) 0	5	15	30	45	60	75	90
CO (L/min)	Medetomidine	IM	4.5 ± 0.6	1.4 ± 0.2*	1.2 ±0.2*	1.0 ± 0.2*	1.1 ± 0.2*	1.0 ± 0.2*	1.1 ± 0.3*	1.1 ± 0.2*
	Combination	IM	4.2 ± 0.9	2.6 ± 0.7*†	2.3 ± 0.4*†	2.0 ± 0.5*†	2.0 ± 0.5*†	1.9 ± 0.4*†	1.8 ± 0.5*†	1.7 ± 0.2*†
	Medetomidine	IV	4.1 ± 0.4	1.1 ± 0.2*	1.2 ± 0.2*	1.3 ± 0.3*	1.3 ± 0.2*	1.3 ± 0.1*	1.4 ± 0.1*	1.3 ± 0.1*
	Combination	IV	4.4 ± 0.7	2.1 ± 0.6*‡	2.0 ± 0.4*‡	1.9 ± 0.4*‡	1.9 ± 0.4*‡	1.7 ± 0.2*‡	1.8 ± 0.3*‡	1.8 ± 0.2*‡
SV (mL)	Medetomidine	IM	48.45 ± 7.72	31.86 ± 16.60*	32.63 ± 9.58*	27.98 ± 7.97*	30.34 ± 6.24*	29.05 ± 6.21*	31.02 ± 8.44*	29.86 ± 5.93*
	Combination	IM	41.42 ± 9.16†	34.28 ± 6.97	35.07 ± 5.74	33.96 ± 5.57*	41.58 ± 6.20	38.38 ± 6.11	39.29 ± 8.88	37.75 ± 5.22
	Medetomidine	IV	43.72 ± 9.23	30.54 ± 9.82*	32.67 ± 5.85*	35.13 ± 6.74*	33.80 ± 3.59*	34.84 ± 3.50*	36.55 ± 4.61	36.03 ± 4.84
	Combination	IV	45.77 ± 4.13	43.84 ± 15.06*	39.60 ± 13.01*	39.69 ± 4.37*	38.30 ± 5.61*	36.55 ± 5.91*	39.00 ± 7.37*	43.89 ± 10.51
SAP (mm Hg)	Medetomidine	IM	172 ± 24	199 ± 23*	197 ± 24*	204 ± 24*	201 ± 21*	196 ± 18*	189 ± 19*	195 ± 14*
	Combination	IM	166 ± 23	185 ± 27*	159 ± 24†	166 ± 22†	166 ± 22†	167 ± 21†	168 ± 18†	167 ± 20†
	Medetomidine	IV	180 ± 32	236 ± 22*	214 ± 17*	197 ± 12*	189 ± 12	190 ± 13	185 ± 17	185 ± 15
	Combination	IV	171 ± 19	203 ± 26*‡	180 ± 23‡	169 ± 15‡	167 ± 17‡	164 ± 15‡	162 ± 18‡	192 ± 0
DAP (mm Hg)	Medetomidine	IM	90 ± 10	106 ± 15*	102 ± 9*	111 ± 8*	110 ± 8*	111 ± 9*	107 ± 9*	103 ± 10*
	Combination	IM	86 ±18	89 ± 11†	73 ± 7*†	75 ± 9*†	75 ± 9*†	78 ± 11†	77 ± 8†	81 ± 8†
	Medetomidine	IV	88 ± 14	134 ± 13*	119 ± 11*	105 ± 11*	102 ± 14*	99 ± 8*	92 ± 4	96 ± 11
	Combination	IV	84 ± 8	98 ± 14*‡	87 ± 10‡	79 ± 7‡	78 ± 6‡	76 ± 5‡	76 ± 10‡	73 ± 6‡
MPAP (mm Hg)	Medetomidine	IM	14 ± 4	18 ± 4*	19 ± 3*	20 ± 4*	21 ± 3*	20 ± 3*	18 ± 2*	17 ± 1*
	Combination	IM	14 ± 3	16 ± 5*	14 ± 4†	15 ± 4†	16 ± 5†	14 ± 3†	14 ± 3†	14 ± 2†
	Medetomidine	IV	13 ± 2	24 ± 3*	21 ± 3*	20 ± 3*	18 ± 1*	19 ± 3*	18 ± 3*	18 ± 3*
	Combination	IV	14 ± 2	18 ± 1*‡	17 ± 2*‡	15 ± 2‡	14 ± 2‡	14 ± 2‡	15 ± 3	13 ± 1

*Within a row, value differs significantly ($P < 0.05$) from the value at time 0. †Within a time point within a variable, value differs significantly ($P < 0.05$) from the value for IM administration of medetomidine alone. ‡Within a time point within a variable, value differs significantly ($P < 0.05$) from the value for IV administration of medetomidine alone.

Table 2—Mean ± SD values for respiratory and blood gas variables at baseline (time 0) and at various time points after IM and IV administration of medetomidine alone or concurrently with MK 0467 (combination) in the same 8 healthy dogs as in Table 1.

Variable	Treatment	Route of administration	Time after administration (min) 0	5	15	30	45	60	75	90
RR (breaths/min)	Medetomidine	IM	17 ± 6	14 ± 5	10 ± 2*	8 ± 2*	6 ± 2*	7 ± 2*	7 ± 2*	6 ± 4*
	Combination	IM	22 ± 11	16 ± 8*	14 ± 5*	9 ± 3*	8 ± 3*	7 ± 3*	6 ± 3*	7 ± 2*
	Medetomidine	IV	18 ± 9	9 ± 4*	7 ± 2*	8 ± 4*	8 ± 4*	7 ± 3*	7 ± 3*	8 ± 3*
	Combination	IV	13 ± 6	11 ± 6*	8 ± 3*	7 ± 3*	7 ± 3*	8 ± 3*	9 ± 7*	7 ± 1*
Pao_2 (mm Hg)	Medetomidine	IM	95.9 ± 5.2	93.8 ± 5.4	92.8 ± 7.2	92.1 ± 8.7	83.1 ± 13.3*	89.9 ± 7.7	88.1 ± 7.6*	87.2 ± 9.9*
	Combination	IM	95.9 ± 7.4	90.0 ± 6.0*	88.1 ± 4.7*	86.3 ± 7.4*	86.6 ± 6.9*	89.9 ± 7.1	83.5 ± 7.1*	87.7 ± 6.3*
	Medetomidine	IV	96.6 ± 8.0	84.8 ± 13.4*	93.1 ± 11.3	86.1 ± 7.7*	88.5 ± 8.2*	90.7 ± 4.3	93.0 ± 5.7	94.2 ± 3.7
	Combination	IV	98.8 ± 8.3	88.8 ± 7.1*	91.1 ± 6.9*	90.1 ± 5.7*‡	92.0 ± 5.2*‡	90.0 ± 4.1*	97.4 ± 7.1‡	92.9 ± 9.6‡
$P\bar{v}o_2$ (mm Hg)	Medetomidine	IM	45.3 ± 4.6	36.2 ± 1.7*	35.3 ± 1.0*	33.5 ± 1.4*	33.7 ± 2.0*	34.8 ± 2.3*	34.5 ± 2.4*	35.6 ± 2.1*
	Combination	IM	41.4 ± 2.1	44.3 ± 4.8†	43.5 ± 2.2†	39.8 ± 2.0†	38.8 ± 1.1†	40.0 ± 2.1†	40.6 ± 2.6†	39.1 ± 2.0†
	Medetomidine	IV	45.0 ± 4.7	33.7 ± 2.0*	35.30 ± 1.7*	35.7 ± 1.4*	36.0 ± 1.7*	37.0 ± 1.9*	36.9 ± 1.7*	37.4 ± 1.8*
	Combination	IV	44.6 ± 3.5	38.9 ± 2.3*‡	41.0 ± 3.2*‡	40.5 ± 2.6*‡	40.5 ± 2.6*‡	40.1 ± 2.9*	39.9 ± 2.9*	40.5 ± 1.6*
Sao_2 (%)	Medetomidine	IM	98.3 ± 0.7	98.0 ± 0.6	97.8 ± 0.8	97.8 ± 1.5	95.9 ± 3.4*	97.6 ± 1.2	97.6 ± 1.3	97.4 ± 1.6
	Combination	IM	98.3 ± 0.8	97.8 ± 1.1	97.9 ± 1.1	97.5 ± 1.7	97.8 ± 1.4†	98.3 ± 1.4	97.8 ± 1.2	98.4 ± 1.5
	Medetomidine	IV	98.2 ± 0.9	95.6 ± 3.4*	97.6 ± 1.6	96.8 ± 1.5*	97.3 ± 1.0	98.0 ± 0.6	98.2 ± 0.8	98.4 ± 0.8
	Combination	IV	98.3 ± 0.5	97.4 ± 1.5‡	97.9 ± 1.0	97.9 ± 0.7‡	98.1 ± 0.6	98.2 ± 0.6	98.6 ± 0.6	98.0 ± 0.6
$S\bar{v}o_2$ (%)	Medetomidine	IM	74.3 ± 5.4	57.3 ± 4.7*	54.5 ± 2.3*	50.6 ± 3.0*	51.6 ± 3.6*	54.0 ± 4.1*	54.7 ± 3.8*	58.3 ± 3.2*
	Combination	IM	69.2 ± 4.7	71.6 ± 7.2†	71.4 ± 4.2†	65.7 ± 4.6*†	65.4 ± 3.6*†	68.2 ± 3.3†	70.6 ± 5.0†	69.1 ± 2.5†
	Medetomidine	IV	73.8 ± 6.4	50.7 ± 1.6*	55.5 ± 1.5*	55.6 ± 2.3*	57.3 ± 1.9*	60.5 ± 2.6*	62.0 ± 2.2*	64.2 ± 2.4*
	Combination	IV	74.1 ± 4.5	64.5 ± 5.7*‡	67.7 ± 5.8*‡	68.1 ± 5.5*‡	69.4 ± 4.9*‡	69.7 ± 4.6*‡	70.2 ± 4.2‡	69.2 ± 0.6
$Paco_2$ (mm Hg)	Medetomidine	IM	38.5 ± 1.3	35.7 ± 2.4	36.4 ± 2.9	33.7 ± 4.3	36.4 ± 5.9	34.4 ± 4.1	35.1 ± 2.5	35.9 ± 2.6
	Combination	IM	37.6 ± 2.8	38.7 ± 1.5†	39.6 ± 1.9†	39.4 ± 2.1†	38.9 ± 1.6†	37.8 ± 2.1†	38.5 ± 2.9†	37.5 ± 3.0
	Medetomidine	IV	36.5 ± 2.4	36.7 ± 3.6	34.4 ± 3.1	37.3 ± 3.5	35.6 ± 3.2	36.4 ± 2.7	35.8 ± 2.7	35.2 ± 1.9
	Combination	IV	37.6 ± 1.7	37.0 ± 3.3	37.1 ± 3.0	37.9 ± 3.0	38.3 ± 2.7	38.6 ± 2.7	36.2 ± 2.4	38.4 ± 2.7
Arterial pH	Medetomidine	IM	7.410 ± 0.020	7.412 ± 0.023	7.402 ± 0.012	7.421 ± 0.029	7.402 ± 0.032	7.412 ± 0.028	7.404 ± 0.015	7.402 ± 0.022
	Combination	IM	7.403 ± 0.013	7.395 ± 0.012*†	7.385 ± 0.016*†	7.384 ± 0.017†	7.390 ± 0.016†	7.394 ± 0.014†	7.394 ± 0.018†	7.402 ± 0.016
	Medetomidine	IV	7.413 ± 0.008	7.393 ± 0.017*	7.402 ± 0.018	7.385 ± 0.013*	7.393 ± 0.011*	7.398 ± 0.012	7.403 ± 0.019	7.399 ± 0.023
	Combination	IV	7.411 ± 0.016	7.402 ± 0.013	7.400 ± 0.019	7.404 ± 0.024	7.402 ± 0.010	7.400 ± 0.013	7.411 ± 0.018	7.392 ± 0.008
Base excess (mmol/L)	Medetomidine	IM	–0.6 ± 1.1	–2.0 ± 1.5	–2.2 ± 1.6	–2.7 ± 1.4	–2.7 ± 1.8	–3.1 ± 1.4	–2.9 ± 1.2	–2.6 ± 0.9
	Combination	IM	–1.4 ± 1.4	–0.9 ± 1.2	–1.3 ± 1.0	–1.6 ± 1.1	–1.4 ± 0.9	–1.8 ± 1.1	–1.4 ± 1.1	–1.4 ± 1.3
	Medetomidine	IV	–1.4 ± 1.4	–2.6 ± 1.2*	–3.4 ± 1.2	–2.8 ± 1.5	–3.3 ± 1.8*	–2.5 ± 1.5	–2.5 ± 1.4	–3.2 ± 1.0
	Combination	IV	–0.8 ± 1.1	–1.9 ± 1.6*‡	–1.8 ± 1.6	–1.1 ± 1.4	–1.0 ± 1.5‡	–0.9 ± 1.5	–1.7 ± 1.6	–1.7 ± 2.2
Arterial Hb (g/dL)	Medetomidine	IM	15.0 ± 1.7	15.9 ± 1.6*	16.2 ± 1.2*	17.0 ± 1.4*	17.3 ± 1.2*	17.1 ± 1.1*	16.9 ± 1.2*	16.9 ± 0.9*
	Combination	IM	15.3 ± 1.1	15.2 ± 0.8	14.6 ± 0.7†	14.3 ± 1.0*†	14.6 ± 1.2†	15.0 ± 1.2†	15.1 ± 1.3†	15.0 ± 1.3†
	Medetomidine	IV	15.1 ± 2.0	18.6 ± 1.4*	18.0 ± 1.4*	17.4 ± 1.2*	16.4 ± 1.0*	16.9 ± 1.2*	16.4 ± 0.9*	16.2 ± 1.1*
	Combination	IV	14.9 ± 1.2	16.1 ± 1.6*	15.6 ± 1.6‡	15.2 ± 1.3‡	15.1 ± 1.3‡	14.8 ± 0.8‡	14.4 ± 1.3‡	14.7 ± 0.4‡
Mixed-venous hemoglobin (g/dL)	Medetomidine	IM	15.1 ± 1.3	15.9 ± 1.3*	16.6 ± 1.8*	17.3 ± 1.0*	17.8 ± 0.8*	17.5 ± 1.1*	17.2 ± 1.1*	16.7 ± 1.3*
	Combination	IM	14.9 ± 1.2	15.1 ± 1.0	14.4 ± 0.7†	13.9 ± 1.2*†	15.1 ± 0.9†	14.9 ± 1.2†	15.2 ± 1.1†	14.8 ± 1.3†
	Medetomidine	IV	15.4 ± 1.2	18.7 ± 1.6*	17.2 ± 1.8*	18.0 ± 1.4*	17.4 ± 1.4*	16.9 ± 1.2*	16.5 ± 1.1*	16.3 ± 1.1*
	Combination	IV	14.7 ± 1.2	15.6 ± 1.1*‡	15.3 ± 1.3‡	15.4 ± 1.4‡	14.5 ± 1.4‡	14.6 ± 1.0	14.4 ± 0.9‡	14.9 ± 0.4
Body temperature (°C)	Medetomidine	IM	37.56 ± 0.46	37.67 ± 0.43*	37.51 ± 0.41	37.53 ± 0.43	37.39 ± 0.41	37.23 ± 0.50*	36.99 ± 0.54*	36.77 ± 0.53*
	Combination	IM	37.74 ± 0.41	37.56 ± 0.37*	37.31 ± 0.49*	37.16 ± 0.40*	36.93 ± 0.33*	36.67 ± 0.29*	36.44 ± 0.33*	36.08 ± 0.27*
	Medetomidine	IV	37.70 ± 0.47	37.93 ± 0.53*	37.70 ± 0.53*	37.45 ± 0.51*	37.20 ± 0.46*	36.93 ± 0.45*	36.67 ± 0.46*	36.30 ± 0.42*
	Combination	IV	37.76 ± 0.67	37.56 ± 0.67*	37.19 ± 0.63*	36.97 ± 0.58*	36.67 ± 0.59*	36.43 ± 0.63*	36.23 ± 0.62*	36.55 ± 0.49*

See Table 1 for key.

Table 3—Mean ± SD values for calculated respiratory variables at baseline (time 0) and at various time points after IM and IV administration of medetomidine alone or concurrently with MK 0467 (combination) in the same 8 healthy dogs as in Table 1.

Variable	Treatment	Route of administration	Time after administration (min) 0	5	15	30	45	60	75	90
Ca_{O_2} (mL/100 mL)	Medetomidine	IM	20.8 ± 2.1	21.9 ± 2.2*	22.3 ± 1.6*	23.4 ± 1.6*	23.3 ± 1.5*	23.4 ± 1.4*	23.2 ± 1.5*	23.1 ± 0.8*
	Combination	IM	21.2 ± 1.7	20.9 ± 1.3	20.2 ± 0.9†	19.7 ± 1.5*†	20.1 ± 1.5†	20.7 ± 1.5†	20.8 ± 1.7†	20.8 ± 1.7†
	Medetomidine	IV	21.0 ± 2.6	24.9 ± 2.3*	24.7 ± 1.9*	23.7 ± 1.7*	22.5 ± 1.5*	23.3 ± 1.6*	22.6 ± 1.1*	22.4 ± 1.5*
	Combination	IV	20.6 ± 1.5	22.0 ± 1.9*‡	21.5 ± 2.1‡	21.0 ± 1.8‡	20.8 ± 1.7	20.4 ± 1.1	20.1 ± 1.8	20.2 ± 0.3
$C\bar{v}_{O_2}$ (mL/100 mL)	Medetomidine	IM	15.8 ± 1.9	12.8 ± 1.6*	12.7 ± 1.6*	12.3 ± 1.2*	12.8 ± 1.3*	13.2 ± 1.4*	13.2 ± 1.1*	13.6 ± 0.9*
	Combination	IM	14.4 ± 1.4	15.3 ± 2.4†	14.4 ± 1.2	12.8 ± 1.1*	13.9 ± 1.0	14.2 ± 1.4	15.0 ± 1.3	14.3 ± 1.4
	Medetomidine	IV	15.9 ± 1.9	13.3 ± 1.4*	13.4 ± 1.4*	14.1 ± 1.4*	14.0 ± 1.4*	14.5 ± 1.4*	14.4 ± 1.5*	14.7 ± 1.3
	Combination	IV	15.2 ± 1.3	14.1 ± 1.4*	14.5 ± 1.4	14.6 ± 1.2	14.1 ± 1.4*	14.2 ± 1.0	14.2 ± 0.8	14.5 ± 0.5
$\dot{V}_{O_2}$ (mL/min/kg)	Medetomidine	IM	7.9 ± 2.2	4.4 ± 0.6*	4.1 ± 0.5*	4.0 ± 1.0*	3.9 ± 0.6*	3.7 ± 0.7*	4.0 ± 0.6*	3.8 ± 0.8*
	Combination	IM	9.2 ± 2.5	4.9 ± 1.3*	4.8 ± 0.8*	4.6 ± 1.0*	4.6 ± 1.4*	4.3 ± 0.8*	3.9 ± 1.1*	4.1 ± 0.5*
	Medetomidine	IV	7.4 ± 3.1	4.7 ± 0.6*	4.8 ± 0.9*	4.5 ± 0.9*	3.9 ± 0.6*	4.2 ± 0.4*	4.1 ± 0.4*	3.8 ± 0.5*
	Combination	IV	8.0 ± 2.0	5.3 ± 1.2*	5.2 ± 2.0*	4.1 ± 0.7*	4.2 ± 0.6*	3.9 ± 0.5*	3.8 ± 1.1*	4.0 ± 0.3*

See Table 1 for key.

ments. However, IV administration of medetomidine and MK 0467 did not cause a significantly higher HR, compared with HR after IV administration of medetomidine alone, at any time point in the study. Also, the duration of differences between IV administration of MK 0467 and medetomidine versus IV administration of medetomidine alone for $P\bar{v}_{O_2}$, ER, CVP, and PAOP was shorter than when the same drugs were given IM. The Pa_{O_2} was significantly higher after IV administration of medetomidine and MK 0467, compared with the Pa_{O_2} after IV administration of medetomidine alone, at 30, 75, and 90 minutes after drug administration.

Discussion

Analysis of results of the study reported here indicated that the peripheral α_2-adrenoceptor antagonist MK 0467, when administered IM or IV concurrently with medetomidine, attenuated the adverse cardiovascular effects typically associated with α_2-adrenoceptor agonist administration. Although it did not prevent changes in cardiovascular variables from baseline values, the receptor antagonist substantially reduced deleterious changes, without any detectable change in the observed sedation. Notably, concurrent IM administration of MK 0467 and medetomidine performed at least as well as IV administration of both drugs for all cardiopulmonary variables. This is particularly relevant for veterinary clinical practice, considering that the IM route of administration is often desirable and it would be inconvenient to have to administer a drug IV before IM administration of a sedative.

In the present study, cardiovascular changes in dogs when concurrently receiving medetomidine and MK 0467 IV were consistent with results of other investigations conducted to evaluate pretreatment of animals with MK 0467 (referred to as L-659,066 in those studies[4,15]) prior to α_2-adrenoceptor agonist administration. Specifically, investigators in 1 study[15] found that the early pressor effects of the α_2-adrenoceptor agonist were blocked in dogs pretreated with MK 0467 (0.2 mg/kg, IV) 30 minutes prior to dexmedetomidine infusion (5 µg/kg over a 15-minute period). In another study[4] conducted by our laboratory group, we also found that pretreatment (IV administration) with the peripheral receptor antagonist at the same dose 5 minutes before medetomidine administration (10 µg/kg, IV) reduced changes in systemic pressures, pulmonary artery pressures, CI, and $P\bar{v}_{O_2}$ from baseline values. In the present study, the same IV dose was used as in that other study[4]; however, medetomidine was administered immediately before MK 0467 administration. The IV dose of MK 0467 in the present study is also similar to that (0.25 mg/kg, IV) concurrently used with dexmedetomidine (10 µg/kg, IV) in another study.[12] Although the dramatic increase in arterial and venous pressures associated with medetomidine was prevented by administration of a peripheral receptor antagonist in the present study, vascular pressures did increase slightly from baseline values.

In the aforementioned study[4] conducted by our laboratory group, we evaluated the short-term effects of IV administration of MK 0467 in dogs. In that study,[4] a small but significant increase in HR and CI was detected but with no change in the other measured variables. In another study,[12] investigators used a higher dose of MK 0467 and found an increase in CI and D_{O_2} with no deleterious effects. In the present study, we chose not to evaluate administration of MK 0467 alone on the basis of results of other studies[4,12,16,17] and in recognition of the fact that the only anticipated clinical use of the receptor antagonist would be in conjunction with the α_2-adrenoceptor agonist.

In the present study, the effectiveness of MK 0467 when administered IM concurrently with medetomidine was of particular interest. At the time of the study, the physiologic effects and pharmacokinetics after IM administration of MK 0467 were unavailable. Because α_2-adrenoceptor agonists are commonly administered IM in clinical practice, we were interested in evaluating the effects of this peripheral receptor antagonist via this route of administration. The dose of medetomidine for IM administration was chosen on the basis of the authors' experience and a report[18] that indicated a dose of 20 µg/kg provides an optimal degree of sedation when medetomidine is used as a premedicant. The authors were unaware of any other studies of the pharmacokinetics or pharmacodynamics after IM administration of MK 0467, so a similar approach (ie, to double the IV dose) was used with the receptor antagonist. The slight superiority of peripheral α_2-adrenocepter blockade after IM administration of the receptor antagonist may

have been attributable to more rapid absorption of the MK 0467, relative to absorption of medetomidine, or a more appropriate dose of the receptor antagonist, relative to the dose of the α_2-adrenoceptor agonist.

We detected a reduction of the measured peripheral vascular effects of medetomidine attributable to the peripheral receptor antagonist, but the typical immediate decrease in HR was not detected when both drugs were administered via the IM route. Despite the maintenance of systemic and pulmonary artery pressures within reference ranges, HR decreased to values typically considered bradycardic, although HRs were above those detected after administration of the α_2-adrenoceptor agonist alone. This finding supports the centrally mediated component of the reduction in HR associated with α_2-adrenoceptor agonist administration and is also consistent with results of other studies.[4,12,13] Consistent with the reduction in HR, all dogs had a reduction in CI and Do_2; however, ER and $P\bar{v}O_2$ were maintained at baseline values for dogs when receiving the peripheral receptor antagonist. This implied that despite the reduction in Do_2, there was an adequate supply of oxygen when dogs received the peripheral receptor antagonist concurrently with the α_2-adrenoceptor agonist. A reduction in CI and Do_2 is not uncommon after administration of sedatives or anesthetics; however, if ER increases, it is indicative of a relative reduction in oxygen supply versus tissue use.

Similar to results of other studies,[4,19–21] arterial blood gas analysis revealed a tendency for mean PaO_2 to decrease after administration of medetomidine in dogs of the present study. The pattern was similar for all treatments, and there were only minor differences between the 2 IV groups at 2 time points. Notably, SaO_2 was > 95% at all time points for all treatments; thus, the alterations were of minor clinical importance. Similarly, some slight differences in $PaCO_2$ were detected when dogs received medetomidine IM; however, values remained within the reference range in all dogs for all treatments throughout the experimental period.

Administration of medetomidine alone to dogs in the present study caused an initial significant increase in body temperature followed by a significant decrease in body temperature, relative to baseline values. The peripheral receptor antagonist prevented the early increase but not the subsequent decrease. A decrease in body temperature following administration of medetomidine has been reported[1,19,22] and has been attributed to decreased muscular activity as well as a direct hypothalamic effect.[23] The fact that the receptor antagonist did not block the decrease in body temperature is consistent with its peripheral action and lack of effect on sedation and the resulting decrease in motor activity. However, the transient increase in body temperature following medetomidine administration was reported in 1 study[21] and was attributed to peripheral vasoconstriction, which resulted in decreased heat loss via peripheral vessels. The researchers in that study[21] proposed a biphasic effect of medetomidine on body temperature, whereby the initial increase is caused by peripheral vasoconstriction and the subsequent decrease is attributed to decreased muscular activity; the findings of the present study supported this proposed effect.

Our observation that sedation quality was unaffected by MK 0467 is in accordance with results of another report[11] in which MK 0467 (referred to as L-659,066) administered IV had no effect on the sedation induced by dexmedetomidine. Although medetomidine, an α_2-adrenoceptor agonist, acts on both central and peripheral receptors, MK 0467 does not cross the blood-brain barrier in rats and marmosets.[24] The lack of effect on centrally mediated sedation in the present study supported the hypothesis that the activity of MK 0467 is similarly restricted to the periphery in dogs or, alternatively, that the receptor antagonist has little affinity for central α_2-adrenoreceptors. The sedation assessment in the present study was limited by the nature of the physiologic measurements performed. Given that MK 0467 had no apparent effect on the sedation caused by medetomidine, a future study with the primary objective of evaluating the sedative characteristics of these drug combinations would be valuable.

Concurrent IM administration of medetomidine and the α_2-receptor antagonist MK 0467 at the dose used in the present study was associated with improvement in cardiopulmonary performance, compared with results after IM administration of medetomidine alone, but there was no detectable effect on the quality of sedation. Given the beneficial effect on cardiopulmonary function when healthy dogs received MK 0467 and medetomidine versus medetomidine alone, it would be interesting to further evaluate whether the beneficial effects of the peripheral receptor antagonist extend to other groups of veterinary patients, such as geriatric or debilitated dogs. To determine additional clinical utility of this peripheral receptor antagonist, studies should be conducted to examine the effect of this receptor antagonist on the analgesic properties of α_2-adrenoceptor agonists.

a. Animal Health Laboratory, Ontario Veterinary College, Guelph, ON, Canada.
b. Domitor, Pfizer Canada Inc, Kirkland, QC, Canada.
c. Provided by Merck & CO Inc, Whitehouse Station, NJ.
d. Diprivan, AstraZeneca Pharmaceuticals Inc, Mississauga, ON, Canada.
e. Aerrane, Baxter Corp, Mississauga, ON, Canada.
f. Lidocaine, AstraZeneca Canada Inc, Mississauga, ON, Canada.
g. Intro-Flex-Percutaneous sheath introducer kit, Edwards Lifescience LLC, Irvine, Calif.
h. Edwards Swan-Ganz, Edwards Lifescience LLC, Irvine, Calif.
i. D5W, Baxter Corp, Mississauga, ON, Canada.
j. DTX Plus pressure transducer systems, Ohmeda Medical Devices, Madison, Wis.
k. ABL 700 series analyzer, Radiometer, Copenhagen, Denmark.
l. S/5 critical care monitor, Datex Ohmeda, GE Healthcare, Helsinki, Finland.
m. Metacam, Boeringer Ingelheim Ltd, Burlington, ON, Canada.
n. SAS Online Doc, version 8, SAS Institute Inc, Cary, NC.

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Appendix

System used for sedation scoring in 8 healthy dogs.

Variable	Score	Description
Posture	1	Standing
	2	Standing but ataxic
	3	Sternally recumbent with head up
	4	Sternally recumbent with head down
	5	Laterally recumbent
Palpebral reflex	1	Medial and lateral present
	2	Medial present but lateral reduced
	3	Medial reduced but lateral absent
	4	Medial and lateral absent
Eye position	1	Central
	2	Partially rotated (> 1/2 of the iris visible)
	3	Fully rotated (< 1/2 of the iris visible)
Jaw tone and tongue manipulation	1	Strong jaw tone; strong resistance to manual attempt to open mouth
	2	Weak resistance to manual attempt to open mouth but resists tongue pull
	3	Weak resistance to manual attempt to open mouth and weak resistance to tongue pull
	4	No jaw tone and no resistance to tongue pull
Response to noise (loud hand clap < 15 cm from ear)	1	Moves head in response to noise
	2	Moves eyes or ears in response to noise
	3	No response

Maximum possible sedation score is 19. Higher scores correspond to greater sedation.