Original Article

Effect of dexmedetomidine combined with pethidine on minimum alveolar concentration of isoflurane in dogs

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Abstract

The effect of dexmedetomidine alone and when combined with pethidine on a minimum alveolar concentration (MAC) of isoflurane was determined in 24 client-owned adult male dogs before castration. Dogs were assigned to Group 1 (n = 12; dexmedetomidine, 5 µg/kg IM) or Group 2 (n = 12; dexmedetomidine, 5 µg/kg and pethidine, 5 mg/kg IM). Sedation and response to noxious stimulation (digit clamping) were evaluated at 15 minutes after drug injection. Then, anaesthesia was induced via a face mask with isoflurane in oxygen and maintained via an endotracheal tube with an end tidal concentration of isoflurane (E´ISO%) of 1%, at the oxygen flow rate of 2 L/min. To determine the isoflurane MAC for each dog, the E´ISO% was increased once the purposeful movement to the noxious stimulation has been detected or decreased if the movement was not detected. The isoflurane MAC was the mean E´ISO% between the highest E´ISO% at which movement was detected and the lowest E´ISO% at which movement was not detected. Cardiorespiratory variables were measured before drug injection until the isoflurane MAC had been determined. The sedation score of Group 2 was found significantly greater than that of Group 1 ($p = 0.0001$). The isoflurane MAC for Group 2 was 0.98 ± 0.24% (mean ± SD) which was significantly lower than 1.31 ± 0.33% for Group 1 ($p = 0.011$). Cardiorespiratory variables did not differ significantly between the groups. In conclusion, dexmedetomidine administered with pethidine provided sedative and sparing effects on the isoflurane MAC which were significantly greater than those of dexmedetomidine alone.

Keywords: dexmedetomidine, dogs, isoflurane, MAC, pethidine

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Introduction

A high anaesthetic concentration is one of the main causes of cardiovascular and respiratory depression during inhalation anaesthesia. The administration of sedative and analgesic drugs prior to or during surgery usually reduces the minimum alveolar concentration (MAC) of an inhalant anaesthetic required to maintain surgical anaesthesia, and may or may not reduce cardiovascular and respiratory complications.

Dexmedetomidine is an α_2-adrenergic agonist which is widely used in small animals to provide sedation, analgesia and muscle relaxation. Important cardiovascular alterations caused by α_2-adrenergic agonists may include hypertension, followed by hypotension, bradycardia, decreased myocardial contractility and perfusion as well as arrhythmias (Dart, 1999). Administration of dexmedetomidine 0.5 and 3 µg/kg IV loading, followed by 0.5 and 3 µg/kg/hour constant rate infusion (CRI) (Pascoe et al., 2006), or 2 µg/kg IV loading followed by 2 µg/kg/hour CRI (Acevedo-Arcique et al., 2014), decreased the MAC of isoflurane in experimental dogs. The isoflurane MAC for dogs receiving dexmedetomidine, 5 µg/kg IM, was less than that of dogs receiving a placebo (distilled water for injection) (Vinyunantakul et al., 2018). To reduce the adverse effects and potentiate the sedative and analgesic effects of α_2-adrenergic agonists, a combination of agents of this drug class with opioids has been investigated. The α_2-adrenergic and opioid receptors are found in close proximity to hippocampal and the spinal cord (Jordan et al., 2003). Each drug acts on different receptors to optimize pain control and to minimize side effects associated with relatively large doses of a single drug. Thus, when used together, the two drug classes are highly synergistic and/or additive for sedation and analgesia. Cardoso et al. (2014) reported that the antinociceptive effect of dexmedetomidine 10 µg/kg IM, combined with methadone 0.5 mg/kg IM or with morphine 0.5 mg/kg IM, was greater than that of dexmedetomidine alone. The end-tidal concentration of isoflurane (E´ISO%) was reduced in dogs receiving buprenorphine 10 µg/kg IV and dexmedetomidine 5 µg/kg IV as premedication, followed by dexmedetomidine 1-3 µg/kg/hour CRI during soft tissue and orthopaedic surgery (Uilenreef et al., 2008).

Pethidine (meperidine) is a mu-opioid receptor agonist and has been used clinically for premedication in dogs and cats. Besides acting at the mu-opioid receptor, pethidine also exerts activity at the α_2-adrenergic receptor subtype responsible for antishivering (Takada et al., 2002). A pethidine dose of 5 mg/kg, administered IM with dexmedetomidine 5 and 10 µg/kg IM, provided greater sedation when compared with each drug alone at the relevant dose rates (Grint et al., 2009). This study aimed to determine the MAC of isoflurane and cardiorespiratory variables after giving dexmedetomidine in combination with pethidine and to compare the results with those after giving dexmedetomidine alone. The hypothesis of this study was that the isoflurane MAC for dogs receiving dexmedetomidine with pethidine was less than that for dogs receiving only dexmedetomidine.

Materials and Methods

Animals: The protocol of this study (No. 1731052) was approved by Chulalongkorn University Animal Care and Use Committee, Bangkok, Thailand. The animals were 24 adult client-owned male dogs of multiple breeds, aged 2-8 years and weighing no more than 10 kg. The experiment was performed before castration of the animal at the Small Animal Hospital of the Faculty of Veterinary Science, Chulalongkorn University. All owners signed a consent form after having been informed the study plan and drugs to be used. All dogs were in good health on the basis of physical examination, CBC, and serum biochemical analyses. The dogs were assigned in alternate sequence into Group 1 (n = 12), receiving dexmedetomidine 5 µg/kg IM, or Group 2 (n = 12), receiving dexmedetomidine 5 µg/kg IM and pethidine 5 mg/kg IM. Sample size was determined from the isoflurane MAC (mean ± SD) of 1.63 ± 0.23 % for dogs not receiving any premedications in our previous study (Vinyunantakul et al., 2018). For a confidence probability of 95%, a minimum of 8 dogs had to be enrolled in each group.

Anaesthesia and monitoring: Food was withheld for at least 12 hours and water for 6 hours prior to the injection of dexmedetomidine alone or in combination with pethidine. Respiratory rate (f_R), electrocardiogram (ECG), heart rate (HR), non-invasive systolic arterial pressure (SAP) and oxygen saturation (SpO_2) were recorded before and 15 minutes after drug injection and during isoflurane MAC determination. Before and 15 minutes after drug injection, f_R and HR were determined from thoracic excursion and auscultation, respectively. With the animal placed in a right lateral recumbency, the SAP was measured non-invasively, using a Doppler flow detector (Model 811, Parks Medical Electronics, Oregon, USA) with a probe placed over the left digital artery of the paw of the front limb and the cuff placed over the left carpus. The ECG (lead II), HR and SpO_2 were monitored during anaesthesia, using a monitoring device (Datascope Passport® V, Mindray DS, New Jersey, USA). At 15 minutes after drug injection, sedation was assessed according to the sedation scoring scale (Table 1), along with the response to the noxious stimulation, by clamping the third or fourth digit of the hind limb, using a 20-cm haemostat forceps whose rubber- covered jaws were closed to the first ratchet. Subsequently, anaesthesia was induced with 4% isoflurane in 4 L/min of oxygen via a face mask. After intubation, all animals were placed in a right lateral recumbency. Anaesthesia was maintained at the end-tidal concentration of isoflurane (E´ISO%) of 1%, with an oxygen flow rate of 2 L/min, through a Bain coaxial breathing system. The E´ISO% and end tidal (ET) CO_2 were measured at the connector

between the Bain breathing circuit and the endotracheal tube, using a Multi-Gas Analyzer (Gas Module 3™, Mindray DS, New Jersey, USA). An anaesthesia ventilator (SAV 2500 Surgivet™, Smiths Medical PM, Wisconsin, USA) was used to maintain the ET CO_2 between 30 and 45 mmHg. Normal body temperature was maintained using a temperature management unit (3M Bair Hugger™ Model 775, 3M Healthcare, Minnesota, USA). Acetated Ringer's solution was administered at a rate of 10 ml/kg/hour.

Table 1 Sedation scoring scale

Score	Descriptive signs
0	Alert with normal startle reaction (head turn towards noise/cringe), standing
1	Less alert but still active, reduced startle reaction (reduced head turn/minimal cringe), if recumbent, animal can rise normally
2	Drowsy, minimal startle reaction, difficult rising if recumbent
3	Very drowsy or stuporous, absent startle reaction, unable to rise

(Modified from Grint et al. (2009) and Valverde et al. (2004[a])).

Determination of minimum alveolar concentration of isoflurane: The E´ISO% was initially set at 1% for at least 15 minutes for anaesthetic equilibration before SAP, HR, SpO_2, isoflurane vaporizer setting, inspired isoflurane concentration, E´ISO% and ET CO_2 were recorded. Then, noxious stimulation was carried out using the technique for isoflurane MAC determination as previously reported by clamping the third or fourth digit of the hind limb, using a 20-cm haemostat forceps whose jaws has been covered with a rubber sleeve (Valverde et al., 2004[b]). The jaws were closed to the first ratchet until a positive motor response was detected or 1 minute had elapsed. The response was considered positive when there was a gross purposeful movement of the head or extremities, including jerking or twisting of the head or movement of the extremities, and was negative if no purposeful movement could be observed. The E´ISO% was increased once the response was positive by 0.1 or 0.2% (for immediate response), or decreased once the response was negative by 0.1%. The new E´ISO% was maintained for at least 15 minutes for anaesthetic equilibration before repeating the noxious stimulation. The isoflurane MAC for that animal was the mean E´ISO% between the highest E´ISO% at which a positive response was detected and the lowest E´ISO% at which the response was not detected. Then, the time to the end of MAC determination (the duration from the injection of dexmedetomidine or dexmedetomidine combined with pethidine until the isoflurane MAC was determined) was recorded. After finishing the isoflurane MAC determination, the animal was castrated.

Statistical analysis: Using Microsoft Office Excel, t-Test: paired two-sample for means (two-tail) was used for comparing data within groups, while t-Test: two-sample assuming equal variances (two-tail) was used for comparing data between groups. Results were considered significantly different when the *p*-value was less than 0.05 and expressed as mean ± SD and median.

Results

Breed, age and weight of dogs in Group 1, receiving only dexmedetomidine, and in Group 2, receiving dexmedetomidine combined with pethidine, are shown in Table 2. There were no significant differences in age or weight of the dogs between groups. Emesis and salivation were not found in any dogs in either group. Dexmedetomidine combined with pethidine produced more sedation than dexmedetomidine alone. The mean sedation score of Group 2 was significantly greater than that of Group 1 ($p = 0.0001$) (Table 2). All dogs responded to noxious stimulation at 15 minutes after injection of either dexmedetomidine alone or in combination with pethidine. Means of the isoflurane MAC and time to end of the isoflurane MAC determination of Group 2 were significantly less than those of Group 1 ($p = 0.011$ and 0.016, respectively) (Table 2).

The f_R means at 15 minutes after drug injection in both groups were significantly lower than the f_R means before drug injection ($p = 0.002$ for Group 1 and $p = 0.02$ for Group 2) (Table 3). However, the lower f_R were still within the clinically acceptable limit. There were no significant differences between groups for the f_R before and at 15 minutes after drug injection. An oxygen saturation level of no less than 95% was observed in all dogs.

The HR of dogs decreased after injection of dexmedetomidine alone or in combination with pethidine (Table 3). The HR means at 15 minutes after drug injection and at right before determining the isoflurane MAC in both groups were significantly lower than the HR before drug injection ($p = 0.003$ and $p = 0.0002$, respectively, for Group 1; $p < 0.0001$ and $p < 0.0001$, respectively, for Group 2). There were no significant differences between the HR measured at 15 minutes after drug injection and at right before determining the isoflurane MAC in either group, and no significant differences between groups for the HR at all measurement points.

In Group 2, the SAP means at 15 minutes after injection of dexmedetomidine combined with pethidine and at right before determining the isoflurane MAC were significantly lower than the SAP mean before drug injection ($p = 0.006$ and $p < 0.0001$, respectively). Only the SAP mean at right before determining the isoflurane MAC in Group 1 was significantly lower than the SAP before the injection of dexmedetomidine ($p = 0.02$) (Table 3). Nevertheless, all of the lower SAP were still within the normal range of the SAP during anaesthesia. The SAP mean at right before determining the isoflurane MAC was significantly

lower than that at 15 minutes after drug injection in both groups (p = 0.035 for Group 1, and p = 0.003 for Group 2). There were no significant differences between groups for the SAP at all measurement points.

Table 2 The number of dogs in each breed, mean ± SD (median) of age, weight, sedation scores, isoflurane MAC, and time to end of isoflurane MAC determination for dogs in Group 1 receiving only dexmedetomidine and Group 2 receiving dexmedetomidine combined with pethidine

Variables	Group 1 (n = 12)	Group 2 (n = 12)
Breeds		
Chi Hua Hua	4	2
Cross	1	2
Pomeranian	2	2
Poodle	1	3
Shih - Tzu	4	3
Age (years)	3.3 ± 2.2 (2.5)	3.9 ± 2.3 (4.0)
Weight (kg)	4.9 ± 2.1 (5.7)	5.1 ± 1.6 (4.9)
Sedation score (0-3)	1.1 ± 0.7 (1)	2.5 ± 0.8 (3)*
Isoflurane MAC (%)	1.31 ± 0.33 (1.30)	0.98 ± 0.24 (0.95)*
Time to end of isoflurane MAC determination (min)	113 ± 43 (108)	69 ± 40 (57)*

(* - significantly different (p <0.05) from Group 1 for each variable).

Table 3 Mean ± SD (median) of respiratory rates (f_R) before and 15 minutes after injection of the compared drugs, heart rate (HR), systolic arterial pressure (SAP) of dogs before and 15 minutes after injection of the compared drugs, and at (right before) the isoflurane MAC determined in Group 1 receiving only dexmedetomidine and Group 2 receiving dexmedetomidine combined with pethidine

Variables	Measurement point	Group 1 (n = 12)	Group 2 (n = 12)
f_R (breath/min)	Before drug injection	72 ± 46 (54)^a	66 ± 50 (53)^a
	15 min after drug injection	30 ± 20 (27)^b	23 ± 15 (20)^b
HR (beats/min)	Before drug injection	108 ± 26 (102)^a	120 ± 36 (114)^a
	15 min after drug injection	74 ± 25 (74)^b	65 ± 28 (56)^b
	At the isoflurane MAC determined	67 ± 16 (71)^b	58 ± 22 (51)^b
SAP (mmHg)	Before drug injection	151 ± 38 (135)^a	156 ± 31 (160)^a
	15 min after drug injection	139 ± 41 (123)^a	125 ± 18 (125)^b
	At the isoflurane MAC determined	114 ± 23 (114)^b	104 ± 16 (101)^c

(^{a,b,c}- values with different superscript letters for each variable in the same column are significantly different (p <0.05)).

Discussion

Dexmedetomidine administered with pethidine provided greater sedation and a significantly lower isoflurane MAC than dexmedetomidine given alone, indicating an additive or synergistic action of pethidine with dexmedetomidine and the sparing effect on the isoflurane MAC of the drug combination. Ossipov et al. (1990) suggest that the interaction between medetomidine, an α_2-adrenoceptor agonist like dexmedetomidine, and opioids in producing antinociception may be additive or synergistic, depending on the route of administration, the ratio administered and the level of processing of the nociceptive input. The interaction is synergistic if the two drugs are given intrathecally and is additive if the two drugs are given systemically. More recently, Chabot-Dore et al. (2015) proposed that the interaction between opioid and α_2-adrenoceptor agonists when co-administered is synergistic (supra-additive). The sedation score in dogs receiving dexmedetomidine combined with pethidine was higher than the score in dogs receiving only dexmedetomidine, supporting the finding of Grint et al. (2009). The authors observed greater sedation after giving dexmedetomidine at a dose of 5 or 10 µg/kg IM in combination with pethidine at a dose of 5 mg/kg IM when compared with administering dexmedetomidine or pethidine alone at the relevant dose rate.

There was no negative control group in the present study. However, a basal isoflurane MAC (mean

± SD) of 1.34 ± 0.11% has been reported in a study using mask induction of anaesthesia with isoflurane and noxious stimulation, similar to the present study (Valverde et al., 2004[b]), while a basal isoflurane MAC (mean ± SD) of 1.58 ± 0.28% has been reported by another study using similar noxious stimulation in dogs receiving anaesthesia induction with propofol (Acevedo-Arcique et al., 2014). In addition, a isoflurane MAC (mean ± SD) of 1.63 ± 0.23% for dogs not receiving any premedications has been reported (Vinyunantakul et al., 2018). Group 1, receiving only dexmedetomidine, could be used as a positive control because the sparing effect of dexmedetomidine on the MAC of isoflurane had already been reported (Bloor et al., 1992; Pascoe et al., 2006; Uilenreef et al., 2008; Acevedo-Arcique et al., 2014; Vinyunantakul et al., 2018). The isoflurane MAC (mean ± SD) for dogs receiving dexmedetomidine combined with pethidine in the present study (0.98 ± 0.24%) was lower than all of the previously reported isoflurane MAC, and that of Group 1 receiving only dexmedetomidine. This indicates that dexmedetomidine combined with pethidine has a sparing effect on the isoflurane MAC.

For other types of noxious stimulation, previously reported isoflurane MAC (mean ± SD) for inhibiting the response of dogs to clamping of the tail after mask anaesthesia induction with isoflurane in oxygen were 1.34 ± 0.11% (Valverde et al., 2004[b]) and 1.69 ± 0.15% (Figueiro et al., 2016); those for inhibiting the response of dogs to electrical stimulation of the buccal mucosa after mask anaesthesia induction with isoflurane in oxygen were 1.80 ± 0.21% (Hellyer et al., 2001) and 1.20 ± 0.17% (Wilson et al., 2006), and after anaesthesia induction with propofol, the isoflurane MAC (mean ± SD) were 1.38 ± 0.08% (Muir III et al., 2003) and 1.41 ± 0.10% (Ueyama et al., 2009). The isoflurane MAC (mean ± SD) for inhibiting the response of dogs to electrical stimulation of the thoracic and pelvic limbs, thoracic limb, pelvic limb and tail, after anaesthesia induction using a mask and isoflurane in oxygen, were 1.51 ± 0.25%, 1.78 ± 0.21%, 1.69 ± 0.23% and 1.75 ± 0.19%, respectively (Pascoe et al., 2006; Figueiro et al., 2016). The isoflurane MAC (mean ± SD) of 0.98 ± 0.24% for dogs receiving dexmedetomidine combined with pethidine in the present study is lower than all of the reported means for the isoflurane MAC. In addition, it is comparable to the 0.90 ± 0.17% reported by a study using similar noxious stimulation, but with propofol anaesthesia induction in dogs receiving a dexmedetomidine IV loading of 2 µg/kg, followed by CRI of 2 µg/kg/hour (Acevedo-Arcique et al., 2014).

Waterman and Kalthum (1989) reported plasma concentration of pethidine of 0.4 µg/ml producing complete analgesia with no response to four applications of finger pressure on the skin wound of acepromazine-atropine premedicated dogs after castration or ovariohysterectomy, and a plasma concentration of above 0.2 µg/ml producing some degree of analgesia to the pressure application. The response was a lifting or turning of the head, a movement of the animal, a cry or whimper, or more than one of these reactions. The two plasma concentrations were maintained for 120 minutes after pethidine 3.5 mg/kg IM. Steffey et al. (1977) reported plasma concentrations of pethidine of above 0.4 µg/ml remaining for 100 minutes and of above 0.2 µg/ml remaining for 180 minutes following pethidine 5.5 mg/kg IM in anesthetized dogs. Therefore, we could say that the analgesic effect of pethidine still remained when the isoflurane MAC was determined in Group 2 at 69 ± 40 minutes after injection of dexmedetomidine and pethidine. For dexmedetomidine, peak sedative and analgesic effects after 20 µg/kg IV were observed at plasma level (mean ±SD) of 14.0 ± 4.5 ng/ml, and analgesia lasted about 1 hour (Kuusela et al., 2000), while its cardiovascular effects lasted for 4 hours (Bloor et al., (1992). In the present study, when the isoflurane MAC was determined in Group 1 at 113 ± 43 minutes after injection of dexmedetomidine, the plasma level of dexmedetomidine must have been very low resulting in low analgesic or sparing effects. Therefore, it is very important when dexmedetomidine is used for premedication that re-dosing is necessary after 60 minutes (Murrell and Hellebrekers, 2005).

Decreased f_R, bradycardia and hypertension, followed by hypotension, are adverse clinical effects of α-2 adrenergic agonists (Pypendop and Verstegen, 1998; Dart, 1999; Sinclair, 2003; Murrell and Hellebrekers, 2005). The combination of dexmedetomidine with some opioids such as butorphanol, buprenorphine (Leppanen et al., 2006), morphine, methadone and tramadol (Cardoso et al., 2014) decreased the f_R of dogs. The f_R in this study was decreased after injection of dexmedetomidine alone or in combination with pethidine. However, the rates were within the clinically acceptable limit and did not differ significantly between groups. Therefore, pethidine did not alter the f_R when compared with the bradypnea induced by dexmedetomidine alone, although opioids can depress respiration by reducing the response to hypercapnia (Steffey et al., 1993). In the present study, none of the dogs was hypercapnic because ET carbon dioxide was controlled by a ventilator, resulting in normal blood gases.

The HR mean at all measurement points in both groups after injection of dexmedetomidine alone or in combination with pethidine was significantly lower was than the HR before drug injection. Bradycardia is the reflex response to the vasoconstrictive effects and a reducing effect on the sympathetic tone (Sinclair, 2003) of the α-2 adrenoreceptor agonist (dexmedetomidine). In addition, the decrease in HR at 15 minutes after drug injection was the result of a lower awareness of the surroundings and lower stimulation due to the sedative effect of dexmedetomidine. In previous studies, HR also decreased in dogs receiving dexmedetomidine alone and dexmedetomidine in combination with morphine, methadone, or tramadol (Cardoso et al., 2014), butorphanol or buprenorphine (Leppanen et al., 2006). In the present study, there were no significant differences in the low HR between Group 1 receiving only dexmedetomidine and Group 2

receiving dexmedetomidine and pethidine. Similarly, Grint et al. (2009) reported that the HR of dogs receiving a combination of IM dose rates of dexmedetomidine and pethidine similar to the present study did not differ from the HR of dogs receiving only dexmedetomidine at 5 or 10 µg/kg IM. Therefore, pethidine does not seem to aggravate the bradycardia induced by the dexmedetomidine. In contrast with Stoelting (1999)'s suggestion on the vagolytic effect of pethidine, this study did not find that pethidine reversed the bradycardia induced by the α-2 adrenergic agonist, supporting the finding of Grint et al. (2009).

Only the SAP mean at right before determining the isoflurane MAC in Group 1, receiving only dexmedetomidine, but all of the SAP means measured after injection of dexmedetomidine combined with pethidine in Group 2 were significantly lower than those before drug injection. However, all of the SAP were within the clinically acceptable limit. The decrease in SAP was the result of bradycardia as the reflex response to the vasoconstrictive effects and the reducing effect on the sympathetic tone of dexmedetomidine (Sinclair, 2003). Interestingly, Congdon et al. (2011) reported that mean arterial pressure was increased in dogs receiving dexmedetomidine at 10 µg/kg IM. Pethidine might not have the effect on vasoconstriction because there were no significant differences in SAP between groups at any of the measurement points. However, the present study did not measure peripheral vascular resistance to support this thought. Similarly, there were no significant differences between the SAP measured before and after administering the combinations of dexmedetomidine with morphine, methadone or tramadol and among the three combinations (Cardoso et al., 2014). The SAP measured at right before determining the isoflurane MAC in both groups were lower than those at 15 minutes after drug injection and before anaesthesia induction, suggesting the effect of isoflurane.

Accuracy of SAP can be affected by indirect measurement of arterial pressure, low HR and low arterial pressure. Moll et al. (2018) recently reported that the SAP measured by Doppler ultrasonography were higher than those measured directly by an invasive technique in dogs weighing less than 5 kg. The closest agreement between the two techniques was found for SAP in normotensive dogs (mean arterial pressure between 60 and 120 mmHg). Although some dogs in the present study weighed less than 5 kg, they were normotensive based on their SAP. Moll et al. (2018)'s study used opioids, sedative, induction anesthetic and the limbs where the Doppler probe and cuff applied were different from the present study.

In conclusion, pethidine enhanced the sedative and analgesic effects of dexmedetomidine and did not exacerbate the bradycardia, hypotension and bradypnea induced by dexmedetomidine alone. Dexmedetomidine administered with pethidine provided sedation and a sparing effect on the isoflurane MAC which were significantly greater than those of dexmedetomidine alone.

Conflicts of Interest: None

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References

Acevedo-Arcique CM, Ibancovichi JA, Chavez JR, Gutierrez-Blanco E, Moran-Munoz R, Victoria-Mora JM, Tendillo-Cortijo F, Santos-Gonzalez M and Sanchez-Aparicio P 2014. "Lidocaine, dexmedetomidine and their combination reduce isoflurane minimum alveolar concentration in dogs." Available: http://www.plosone.org. Accessed September, 2014, 9(9) e106620.

Bloor BC, Frankland M, Alper G, Raybould D, Weitz J and Shurtliff M 1992. Hemodynamic and sedative effects of dexmedetomidine in dog. J Pharmacol Exp Ther. 263(2): 690-697.

Boscan P, Monnet E, Mama K, Twedt DC, Congdon J, Eickhoff JC and Steffey EP 2011. A dog model to study ovary, ovarian ligament and visceral pain. Vet Anaesth Analg. 38: 260-266.

Cardoso CG, Marques DRC, da Silva THM and de Mattos-Junior E 2014. Cardiorespiratory, sedative and antinociceptive effects of dexmedetomidine alone or in combination with methadone, morphine or tramadol in dogs. Vet Anaesth Analg. 41: 636-643.

Chabot-Dore AJ, Schuster DJ, Stone LS and Wilcox G 2015. Analgesic synergy between opioid and α_2-adrenoceptors. Br J Pharmacol. 172: 388-402.

Congdon JM, Marquez M, Niyom S and Boscan P 2011. Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs. J Am Vet Med Assoc. 239(1): 81-89.

Dart CM 1999. Advantages and disadvantages of using alpha-2 agonists in veterinary practice. Aust Vet J. 77(11): 720-721.

Figueiro MR, Soares JHN, Ascoli FO, Were S and de Segura IAG 2016. Isoflurane MAC determination in dogs using three intensities of constant-current electrical stimulation. Vet Anaesth Analg. 43: 464-471.

Grint NJ, Burford J and Dugdale AHA 2009. Does pethidine affect the cardiovascular and sedative effects of dexmedetomidine in dogs? J Small Anim Pract. 50: 62-66.

Hellyer PW, Mama KR, Shafford HL, Wagner AE and Kollias-Baker C 2001. Effect of diazepam and flumazenil on minimum alveolar concentration for dogs anesthetized with isoflurane or a combination of isoflurane and fentanyl. Am J Vet Res. 62(4): 555-560.

Jordan BA, Gomes I, Rios C, Filipovska J and Devi LA 2003. Functional interactions between μ opioid and α_{2A} -adrenergic receptors. Mol Pharmacol. 64(6): 1317-1324.

Kuusela E, Raekallio M, Anttila M, Falck I, Molsa S and Vainio O 2000. Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Ther. 23(1): 15-20.

Leppanen MK, McKusick BC, Granholm MM, Westerholm FC, Tulamo R and Short CE 2006. Clinical efficacy and safety of dexmedetomidine and buprenorphine, butorphanol or diazepam for canine hip radiograph. J Small Anim Pract. 47: 663-669.

Matsubara LM, Oliva VNLS, Gabas DT, Oliveira GCV and Cassetari ML 2009. Effect of lidocaine on the minimum alveolar concentration of sevoflurane in dogs. Vet Anaesth Analg. 36: 407-413.

Moll X, Aguilar A, Garcia F, Ferrer R and Andaluz A 2018. Validity and reliability of Doppler ultrasonography and direct arterial blood pressure measurements in anaesthetized dogs weighing less than 5 kg. Vet Anaesth Analg. 45: 135-144.

Muir III WW, Wiese AJ and March PA 2003. Effects of morphine, lidocaine, ketamine, and morphine-lidocaine-ketamine drug combination on minimum alveolar concentration in dogs anesthetized with isoflurane. Am J Vet Res. 64(9): 1155-1160.

Murrell JC and Hellebrekers LJ 2005. Medetomidine and dexmedetomidine: a review of cardiovascular effects and antinociceptive properties in the dog. Vet Anaesth Analg. 32: 117–127.

Ossipov MH, Harris S, Lloyd P, Messineo E, Lin BS and Bagley J 1990. Antinociceptive interaction between opioids and medetomidine: systemic additivity and spinal synergy. Anesthesiology. 73: 1227-1235.

Pascoe PJ, Raekallio M, Kuusela E, McKusick B and Granholm M 2006. 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.

Pypendop BH and Verstegen JP 1998. Hemodynamic effects of medetomidine in the dog: a dose titration study. Vet Surg. 27: 612-622.

Sinclair MD 2003. A review of the physiological effects of α_2-agonists related to the clinical use of medetomidine in small animal practice. Can Vet J. 44: 885-897.

Steffey EP, Martucci R, Howland D, Asling JH and Eisele JH 1977. Meperidine – halothane interaction in dogs. Canad Anaesth Soc J. 24(4): 459-467.

Steffey EP, Eisele JH, Baggot JD, Woliner MJ, Jarvis KA and Elliott AR 1993. Influence of inhaled anesthetics on the pharmacokinetics and pharmacodynamics of morphine. Anesth Analg. 77(2): 346-351.

Stoelting RK 1999. Pharmacology and Physiology in Anesthetic Practice. 3rd ed. Philadelphia: Lippincott-Raven 814pp.

Takada K, Clark DJ, Davies MF, Tonner PH, Krause TKW, Bertaccini E and Maze M 2002. Meperidine exerts agonist activity at the α_{2B}-adrenoceptor subtype. Anesthesiology. 96: 1420-1426.

Ueyama Y, Lerche P, Eppler CM and Muir WW 2009. Effect of intravenous administration of perzinfotel, fentanyl, and a combination of both drugs on the minimum alveolar concentration of isoflurane in dogs. Am J Vet Res. 70(12): 1459-1464.

Uilenreef JJ, Murrell JC, McKusick BC and Hellebrekers LJ 2008. Dexmedetomidine continuous rate infusion during isoflurane anaesthesia in canine surgical patients. Vet Anaesth Analg. 35: 1–12.

Valverde A, Cantwell S, Hernandez J and Brotherson C 2004[a]. Effect of acepromazine on the incidence of vomiting associated with opioid administration in dogs. Vet Anaesth Analg. 31(1): 40-45.

Valverde A, Doherty TJ, Hernandez J and Davies W 2004[b]. Effect of lidocaine on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg. 31: 264-271.

Vinyunantakul K, Durongphongtorn S and Kalpravidh M 2018. Effect of dexmedetomidine on isoflurane minimum alveolar concentration in dogs. Thai J Vet Med. 48(Suppl): 49-51. Proceedings of the 17th Chulalongkorn University Veterinary Conference. Impact Exhibition and Convention Center, Bangkok, Thailand, April 25-27, 2018.

Waterman AE and Kalthum W 1989. Pharmacokinetics of intramuscularly administered pethidine in dogs and the influence of anaesthesia and surgery. Vet Rec. 124: 293-296.

Wilson D, Pettifer GR and Hosgood G 2006. Effect of transdermally administered fentanyl on minimum alveolar concentration of isoflurane in normothermic and hypothermic dogs. J Am Vet Med Assoc. 228(7): 1042-1046.