Potential use of dexmedetomidine for different levels of sedation, analgesia and anaesthesia in dogs

R.A. Ahmad, Amarpal, P. Kinjavdekar, H.P. Aithal, A.M. Pawde, D. Kumar

Indian Veterinary Research Institute, Izatnagar, India

ABSTRACT: A combination of drugs may be preferred over the use of a single agent to induce deep sedation. A synergistic interaction between the drugs reduces the dose requirements of the drugs thereby minimising the unwanted side effects associated with each drug and improving recovery. The present study was undertaken to evaluate the suitability of dexmedetomidine and dexmedetomidine in combination with midazolam-fentanyl or midazolam-fentanyl-ketamine for different levels of sedation, analgesia and anaesthesia in dogs. In a prospective, blinded, randomised clinical trial, 12 mixed breed dogs were divided into three groups. Animals of Group I were injected with dexmedetomidine 20 µg/kg. Animals of Group II received 20 µg/kg dexmedetomidine + 0.2 mg/kg midazolam + 4 µg/kg fentanyl and animals of Group III were administered with 20 µg/kg dexmedetomidine + 0.2 mg/kg midazolam + 4 µg/kg fentanyl + 10 mg/kg ketamine. All the drugs were given simultaneously via the intramuscular route. Jaw relaxation, palpebral reflex, pedal reflex and response to intubation were recorded and graded on a numerical scale. Values of heart rate, respiratory rate, rectal temperature and mean arterial pressure were recorded at baseline and then at predetermined intervals up to 120 min. Onset of sedation time, onset of recumbency time, time to return of righting reflex, standing recovery time and complete recovery time were recorded. Maximal muscle relaxation, sedation and analgesia were observed in animals of Group III, which was followed in decreasing order by Groups II and I. Heart rate decreased significantly ($P < 0.05$) after administration of drugs in Groups I and II but a significant ($P < 0.05$) increase was recorded in Group III. Respiratory rate decreased significantly ($P < 0.05$) in all the groups. Rectal temperature decreased non-significantly in all the groups. Mean arterial pressure initially increased significantly ($P < 0.01$) in Groups I and III followed by a decrease in Group I, but in Group III it remained above the base line. In Group II, MAP decreased throughout the study period. Onset of sedation time and onset of recumbency time were significantly ($P < 0.05$) shorter in Group III as compared to Group I. Time to return of righting reflex, standing recovery time and complete recovery time did not differ significantly between the groups. It is concluded that dexmedetomidine provides a reliable moderate sedation and analgesia. Addition of midazolam and fentanyl enhances sedation, analgesia and muscle relaxation induced by dexmedetomidine. Addition of ketamine produced deep sedation and complete anaesthesia with lesser cardiopulmonary depression. Thus, dexmedetomidine can be used safely in combination with midazolam, fentanyl and ketamine for different levels of sedation, analgesia and anaesthesia in dogs.

Keywords: dexmedetomidine; analgesia; anaesthesia; ketamine; fentanyl; midazolam; dogs

In canine practice different levels of sedation and analgesia may be obtained by the use of a number of drugs, including alpha-2 agonists. Among alpha-2 agonists, dexmedetomidine, an active optical isomer of medetomidine (MacMillan et al. 1996), is a safe drug for sedation in dogs but its effect has been described to plateau. Thus, increasing its dose does not result in a parallel increase in the depth of sedation but rather side effects become pronounced (Kuusela et al. 2000). Practically, therefore, it may be advisable to use drugs of other pharmacological groups together with dexmedetomidine for increasing the depth of sedation and analgesia or inducing anaesthesia.

Benzodiazepines have synergistic interactions with alpha-2 agonists (Bol et al. 2000); thus, they may be a logical choice for increasing the depth of dexmedetomidine-induced sedation. Midazolam is

a water soluble imidazole benzodiazepine derivative with minimal cardiopulmonary effects (Pypendop and Verstegen 1994; Lemke 2007). Similarly, combinations of opioids with alpha-2 agonists may induce profound analgesia and sedation (Tranquilli et al. 1990). Fentanyl, a synthetic μ opioid having minimal effects on the cardiac output and blood pressure (Thurmon et al. 1999), may also be a logical choice for increasing the depth of analgesia. The use of ketamine has been widely recommended with alpha-2 agonists as the two drugs are complimentary to each other, while potentiating the analgesia, the side effects are minimised (Posner and Burns 2009).

The aim of the study was to investigate the possibility of different levels of sedation, analgesia and anaesthesia and associated effects produced by dexmedetomidine and dexmedetomidine in combination with midazolam, fentanyl and ketamine in dogs.

MATERIAL AND METHODS

Twelve client-owned mixed breed dogs of either sex (mean weight 17.44 ± 0.84 kg; age 24.44 ± 1.53 months), were used for the study. In a prospective randomised blinded design the dogs were divided into three Groups, I, II and III of four animals each. An informed consent was obtained from the animal owners prior to start of the study.

In the animals of Group I, dexmedetomidine alone at 20 μg/kg (0.5 mg/ml, Orion Pharma, Turku, Finland) was administered. In the animals of Group II, a combination of dexmedetomidine 20 μg/kg, midazolam 0.2 mg/kg (5 mg/ml, Neon Laboratories, Thane, India) and fentanyl 4 μg/kg (50 mg/ml, Sun Pharmaceutical, India) were injected and in the animals of Group III, dexmedetomidine 20 μg/kg, midazolam 0.2 mg/kg, fentanyl 4 μg/kg and ketamine 10 mg/kg (50 mg/ml, Themis Medicare, Uttarakhand, India) were administered. All the drugs were injected simultaneously via the intramuscular route using separate syringes. The animals were left undisturbed for 10 min to allow the onset of effects and then subsequent observations were made up to 120 min. The doses used in the current study were based on the results of earlier studies (Thurmon et al. 1999; Kuusela 2004; Lemke 2007).

Observations

Jaw relaxation, palpebral reflex, pedal reflex and response to intubation were recorded at 0 (base value), 10, 15, 20, 30, 45, 60, 75, 90, 105 and 120 min after administration of drugs in all the groups. Relaxation of the jaw, taken as a measure of muscle relaxation, was scored by observing the resistance to opening of the jaw while pulling apart the lower and upper jaws (Table 1). The status of the palpebral reflex was recorded as a measure of depth of sedation (Leppanen et al. 2006). It was scored by observing a blink of the eye lids on touching the area around the medial canthus of the eyes with the index finger (Table 1). The status of the pedal reflex, recorded as a measure of the depth of analgesia, was scored by observing the withdrawal reflex to the pinching of the inter-digital skin of the hind foot of the animal (Table 1). Response to intubation was recorded to assess the feasibility of intubation (Table 1). If the animal allowed easy in-

Table 1. System of recording of various reflexes and responses

Parameter	Score				
	0	1	2	3	4
Relaxation of jaw	did not allow opening of the jaws	resistant to opening of the jaws and closed quickly	less resistance to opening of the jaws and closed slowly	no resistance and jaws remain open	–
Palpebral reflex	intact and strong (quick blink)	intact but weak (slow response)	very weak (very slow and occasional response)	Abolished (no response)	–
Pedal reflex	intact and strong (strong withdrawal)	intact but weak (animal responding slowly)	intact but very light (slow and occasional response)	abolished completely (no response)	–
Response to intubation	did not permit entry of tube into the mouth	allowed entry but chewed	allowed deeper entry but coughed	difficult intubation with coughing	easy intubation without coughing

tubation, the endotracheal tube was left *in situ* and return of the laryngeal reflex was recorded when the animal started coughing.

Heart rate (beats/min) and MAP (mmHg) were recorded using a non-invasive blood pressure monitor (Surgivet®, Smith's medical, USA), respiratory rate (breaths/min) was determined by counting thoraco-abdominal excursions and rectal temperature (°C) was measured using a digital thermometer, up to 120 min.

Onset of sedation time was determined as the time elapsed from time of injection of the drugs to the time of onset of drowsiness. Onset of recumbency time was recorded as the time elapsed from the time of injection of the drugs to the time when the animal became recumbent.

Time to return of righting reflex was determined as the time elapsed from the injection of drugs to the time when the animal could regain sternal recumbency. Standing recovery time was determined as the time elapsed from the time of injection of the drugs to the time when the animal could attain standing position. Complete recovery time was determined as the time elapsed from injection of the drugs to the time when the animal could stand and walk unassisted. Duration of anaesthesia was determined as the time that elapsed from the time of abolition of the pedal reflex to the time when it reappeared.

Statistical analysis

Data were analysed using SPSS software version 15.0 (SPSS, Inc., Chicago, IL). Means at different time intervals among different groups were compared using one way analysis of variance (ANOVA) and Duncan's multiple range test (DMRT). Mean values at different intervals were compared with their base values using the paired *t*-test. The subjective data generated from the scoring of various parameters were analysed using the Kruskal-Wallis test. In each analysis, the differences were considered significant at a value of $P < 0.05$.

RESULTS

Muscle relaxation scores were minimal in Group I, intermediate in Groups II and maximal in Group III (Figure 1). At the 20 min interval muscle relaxation scores in Groups II and III were significantly ($P < 0.05$) higher than those in Group I. The palpebral reflex scores were minimal in Group I, intermediate in Group II and maximal in Group III but the differences in palpebral reflex score among the groups were not significant (Figure 2). The highest pedal reflex scores were recorded in the animals of Group III followed, in decreasing order, by Groups II and I (Figure 3). Complete loss of pedal reflex was recorded from 10 to 20 min in Group III suggesting a time in anaesthesia of about 10 min.

The laryngeal reflex was intact in Group I and none of the animals permitted intubation. In Groups II and III, laryngeal reflexes were lost completely and all the animals permitted easy intubation. The intubation scores at 20, 30 and 45 min intervals were significantly greater in Groups II and III than those in Group I (Figure 4).

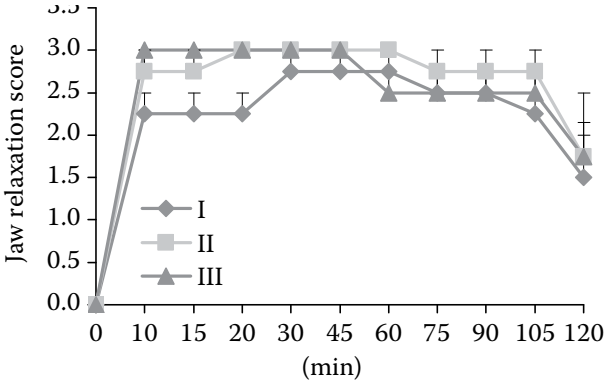

Figure 1. Mean ± SE jaw relaxation scores after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III) ($n = 4$)

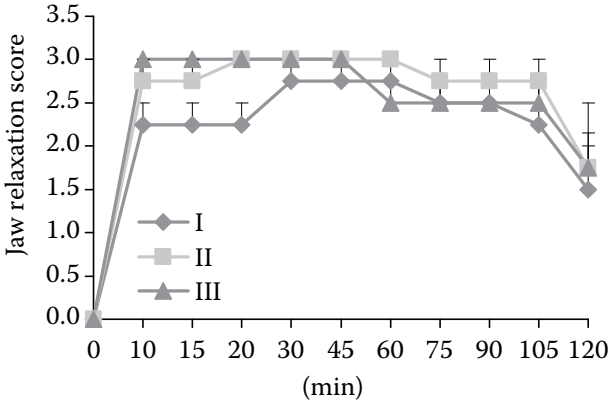

Figure 2. Mean ± SE palpebral reflex scores after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl ketamine (Group III) ($n = 4$)

Table 2. Mean ± SE values of heart rate after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III)

Group	Time intervals (min)										
	0	10	15	20	30	45	60	75	90	105	120
I	106.80 ± 14.19	42.75 ± 2.05*a	37.75 ± 3.75*a	38.50 ± 0.48*a	38.00 ± 1.78*a	36.25 ± 2.36*a	36.50 ± 2.47*a	37.25 ± 2.29*a	44.50 ± 5.90*a	44.00 ± 5.01*a	43.50 ± 4.17*a
II	115.80 ± 6.61	39.50 ± 0.87**b	37.75 ± 1.44**a	37.00 ± 1.78**a	34.75 ± 2.87**a	37.50 ± 2.40**a	36.25 ± 1.65**a	35.50 ± 4.13**a	38.75 ± 1.80**a	34.00 ± 3.24**a	41.75 ± 6.81*a
III	85.50 ± 3.78	93.25 ± 5.30*c	90.00 ± 3.24b	86.00 ± 3.87b	75.50 ± 4.29b	70.00 ± 3.38*b	65.25 ± 8.63*b	67.00 ± 1.47*b	64.50 ± 3.80*b	65.25 ± 6.02*b	64.75 ± 6.20*b

Values with different letters differ significantly ($P < 0.05$) at corresponding intervals
*differ significantly ($P < 0.05$) from respective baseline values
**differ significantly ($P < 0.01$) from respective baseline values

Vomiting was recorded in one animal each of Group I and Group III.

Heart rate (HR) decreased significantly ($P < 0.05$) until the end of the observation period in Groups I and II. In contrast, an initial increase in heart rate was recorded in the animals of Group III. In Group III HR also decreased gradually at subsequent intervals and dropped significantly below the baseline values. However, HR in Group III remained significantly higher than the values in Groups I and II (Table 2).

Respiratory rate (RR) decreased in all the groups after administration of the drugs and remained lower than the baseline values up to the end of the study period. RR did not differ significantly ($P > 0.05$) between the groups at any time interval (Table 3).

An initial non-significant increase in rectal temperature (RT) was observed in all groups, which decreased towards the end of the study. However, differences between the groups were not significant (Table 4).

In Group I mean arterial pressure (MAP) increased significantly ($P < 0.01$) initially at the 10 min interval and then decreased gradually to drop significantly ($P < 0.05$) below the baseline at 60 min. In contrast, in Group II, MAP decreased gradually to dip significantly below the baseline at 60 min. MAP in Group III increased significantly ($P < 0.01$) at 10 min and remained elevated throughout the study period. Towards the end of the study, an improvement in MAP was also seen in both Groups I and II. MAP in Group III remained significantly higher after drug administration as compared to Groups I and II (Table 5).

Time for onset of sedation and recumbency time were shortest in the animals of Group III as compared to Groups I and II. Both onset of sedation and time of recumbency were significantly ($P <$

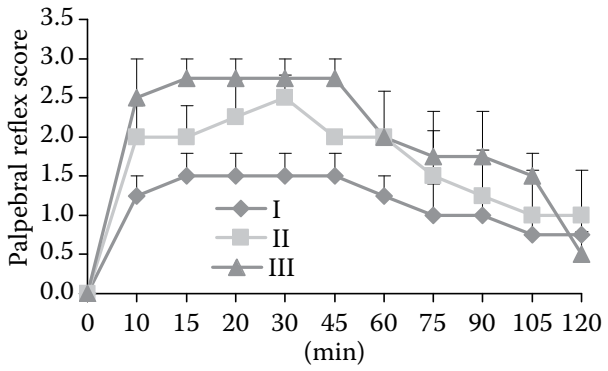

Figure 3. Mean ± SE pedal reflex scores after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III) ($n = 4$)

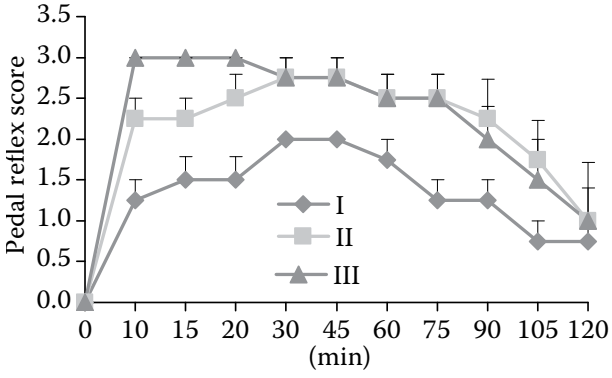

Figure 4. Mean ± SE response to intubation scores after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III) ($n = 4$)

Table 3. Mean ± SE values of respiratory rate after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III)

Group	Time intervals (min)										
	0	10	15	20	30	45	60	75	90	105	120
I	34.50 ± 7.54	15.00 ± 2.65*	13.25 ± 0.85	13.00 ± 1.35	14.00 ± 1.78*	13.75 ± 2.50*	13.75 ± 3.00*	14.00 ± 2.65*	14.00 ± 3.37*	14.50 ± 4.25*	19.75 ± 8.75*
II	26.25 ± 4.33	16.50 ± 2.87	13.00 ± 2.12	11.25 ± 1.65	9.25 ± 2.29*	10.50 ± 1.71	11.25 ± 2.06	11.00 ± 1.87	11.50 ± 1.85	10.75 ± 2.14	10.75 ± 2.14
III	25.00 ± 3.03	10.00 ± 0.41*	10.75 ± 1.18*	10.00 ± 0.82*	11.25 ± 1.25*	11.50 ± 1.2*	14.00 ± 1.47*	15.00 ± 0.71*	15.50 ± 0.96*	16.25 ± 0.63*	18.25 ± 1.32*

Values with different letters differ significantly ($P < 0.05$) at corresponding intervals
*differ significantly ($P < 0.05$) from respective baseline values
**differ significantly ($P < 0.01$) from respective baseline values

Table 4. Mean ± SE values of rectal temperature (°C) after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III)

Group	Time intervals (min)										
	0	10	15	20	30	45	60	75	90	105	120
I	38.96 ± 0.09	39.11 ± 0.11^{a}	38.87 ± 0.32	38.94 ± 0.32^{ab}	38.94 ± 0.07^{a}	38.94 ± 0.12^{a}	38.71 ± 0.03*^{a}	38.13 ± 0.24*	38.10 ± 0.25*	38.00 ± 0.31	37.85 ± 0.34
II	38.71 ± 0.32	39.08 ± 0.14^{a}	38.95 ± 0.16	39.10 ± 0.12^{a}	38.84 ± 0.21^{a}	38.63 ± 0.10^{b}	38.18 ± 0.08^{b}	37.92 ± 0.12	37.42 ± 0.32	37.51 ± 0.27	37.25 ± 0.26
III	38.27 ± 0.05	38.42 ± 0.07^{b}	38.35 ± 0.12	38.36 ± 0.04^{b}	38.22 ± 0.08^{b}	38.19 ± 0.10^{c}	37.99 ± 0.24^{b}	37.71 ± 0.34	37.65 ± 0.35	37.60 ± 0.34	37.46 ± 0.35

Values with different letters differ significantly ($P < 0.05$) at corresponding intervals
*differ significantly ($P < 0.05$) from respective baseline values
**differ significantly ($P < 0.01$) from respective baseline values

Table 5. Mean ± SE values of mean arterial pressure (mmHg) after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III)

Group	Time intervals (min)										
	0	10	15	20	30	45	60	75	90	105	120
I	107.00 ± 5.00	136.30 ± 4.77**^{a}	127.00 ± 3.99**^{a}	117.50 ± 3.23*^{a}	111.80 ± 2.75	102.80 ± 2.50	96.25 ± 2.02*	102.50 ± 3.10	103.50 ± 2.63^{a}	106.00 ± 4.08	104.80 ± 5.41
II	119.00 ± 3.90	117.80 ± 4.66^{b}	117.00 **±4.10***^{a}	112.00 ± 7.13^{a}	112.80 ± 4.66*	107.80 ± 8.04	107.00 ± 4.64*	104.80 ± 5.07*	98.00 ± 3.98**^{a}	101.50 ± 9.29	111.80 ± 8.33
III	104.50 ± 4.35	163.00 ± 3.14**^{c}	150.80 ± 5.42*^{b}	134.00 ± 4.37*^{b}	123.00 ± 2.87**	117.50 ± 2.40*	107.80 ± 5.04	112.80 ± 6.16	118.50 ± 2.87^{b}	117.00 ± 3.24	117.00 ± 3.03

Values with different letters differ significantly ($P < 0.05$) at corresponding intervals
*differ significantly ($P < 0.05$) from respective baseline values
**differ significantly ($P < 0.01$) from respective baseline values

0.05) shorter in Group III than in Group I but did not differ significantly from Group II. Time to return of righting reflex, standing recovery time and complete recovery time did not differ significantly between the groups (Table 6).

DISCUSSION

Midazolam, fentanyl and ketamine were chosen for administration along with dexmedetomidine with consideration of their synergism with dexme-

Table 6. Mean± SE of time of onset of sedation, onset of sedation, time to return of righting reflex, standing recovery time, complete recovery time (min) after administration of dexmedetomidine (Group I), dexmedetomidine-midazolam-fentanyl (Group II) and dexmedetomidine-midazolam-fentanyl-ketamine (Group III)

Group	Weak time	Down time	Time to righting reflex	Standing recovery time	Complete recovery time
I	4.5 ± 0.96[a]	6.75 ± 0.84[a]	131.3 ± 9.47	144.3 ± 9.01	164.3 ± 10.38
II	2.5 ± 0.29[ab]	5.25 ± 1.03[ab]	140.5 ± 9.24	150 ± 9.98	167.3 ± 10.04
III	1.5 ± 0.29[b]	2.50 ± 0.29[b]	142.5 ± 11.61	165.8 ± 11.56	183.8 ± 11.37

Values with different letters differ significantly ($P < 0.05$) between the groups

detomidine and their minimal side effects. The aim of administering multiple drugs was to achieve variable levels of sedation, muscle relaxation, analgesia and anaesthesia that would meet clinical demands in a variety of diagnostic and therapeutic procedures without major side effects. The doses used in the current study were based on the results of earlier reports (Thurmon et al. 1999; Kuusela 2004; Lemke 2007).

Dexmedetomidine alone induced moderate muscle relaxation, which was increased further in Groups II and III. All alpha-2 agonists, including dexmedetomidine are known to induce good muscle relaxation through the inhibition of intraneuronal transmission of impulses at the level of the CNS (Gross 2001; Lemke 2007). Better muscle relaxation in Groups II and III could be attributed to the addition of midazolam (Lemke 2007).

Dexmedetomidine induces a dose dependent sedation (Sabbe et al. 1994) but increasing the dose beyond a certain level does not cause a further increase in sedation (Kuusela et al. 2001). The status of the palpebral reflex was used as a measure of sedation as has been reported in earlier studies (Leppanen et al. 2006). In the present study it also allowed confident prediction of CNS depression. The only mild sedation in the animals of Group I conformed to the findings of Ko et al. (2000), who did not advocate the use of medetomidine alone for sedation of dogs undergoing moderately to severely painful procedures. Deep sedation (higher score) in Groups II and III could be attributed to the additive or synergistic action of the midazolam, dexmedetomidine and ketamine. A greater depth of sedation has been reported using midazolam-ketamine and medetomidine-ketamine compared to midazolam or medetomidine alone (Jacobson and Hartsfield 1993).

The depth of analgesia was evaluated by measuring the withdrawal reflex as it is easy to determine and repeat, and does not result in tissue destruction and sensitisation after numerous repetitions (Kuusela 2004). Analgesia induced by dexmedetomidine is mediated at the spinal level (Hayashi et al. 1995), where it interrupts nociceptive pathways to the ventral root of the dorsal horn, thus reducing the spinal reflex (Kending et al. 1991; Savola et al. 1991). Thus, the withdrawal reflex is considered a valid parameter when evaluating α_2-agonist-mediated analgesia (Kuusela 2004).

The antinociception induced by alpha-2 agonists may be due, in part, to acetylcholine release in the spinal cord (Klimscha et al. 1997). In the present study the pedal reflex was not completely abolished in the animals of Group I and was in agreement with the observations of Ko et al. (2001). The increased analgesia in Group II could be attributed to the action of fentanyl (Thurmon et al. 1999) and the reported synergistic interaction between alpha-2 agonists and opioids (Salmenpera et al. 1994; Amarpal et al. 1996). The complete anaesthesia between 10 and 20 min in the animals of Group III can be explained by the action of ketamine, mediated through the interruption of ascending transmission from those parts of the brain responsible for unconscious and conscious functions (Lin 2007).

The mild depression of the laryngeal reflex in Group I might be attributable to the hypnotic action of dexmedetomidine following its binding to α_{2A} -adrenoreceptors in the locus coeruleus (Chiu et al. 1995). In Group II, complete depression of the laryngeal reflex occurred leading to intubation at 30 min, which corresponded to the time of the peak effect of fentanyl (Thurmon et al. 1999). A combined action of dexmedetomidine and midazolam with fentanyl could be responsible for abolition of the reflex (Salmenpera et al. 1994; Lin 2007). In Group III, by 20 min easy intubation was possible in all the animals. Although laryngeal and pharyngeal reflexes are reasonably well maintained during ketamine-induced anaesthesia in all species (Haskins et al. 1975), the addition of alpha-2 agonists, benzodiazepine and opioids greatly diminish these reflexes (Ko et al. 2000).

Vomiting was recorded in one animal each from Groups I and III. Vomiting after administration of alpha-2 agonists is mainly attributed to activation of the chemoreceptor trigger zone (CTZ). It has been recorded that alpha-2 adrenoreceptors are involved in the mediation of emetic action in CTZ and this does not involve beta adrenergic, cholinergic, dopaminergic, serotonergic and opioid receptors in the emetic pathway (Hikasa et al. 1992).

The decrease in heart rate recorded in Group I might be attributed to reflex bradycardia as a result of alpha-2 agonist-induced vasoconstriction (Lemke 2007). The bradycardia observed in the present study supported the findings of earlier studies in dogs (Kuusela et al. 2000) and swine (Sano et al. 2010). The further decrease in the heart rate in Group II could be due to the action of fentanyl (Thurmon et al. 1999). Fentanyl and its synergistic interaction with dexmedetomidine and midazolam may increase the degree of bradycardia induced by dexmedetomidine (Salmenpera et al. 1994). The initial increase in the heart rate in Group III might be down to the stimulatory effects of ketamine on the heart rate (Zielmann et al. 1997). Ketamine has been reported to oppose the bradycardiac effects of dexmedetomidine (Shukry and Miller 2010).

The decrease in RR in Group I was in agreement with the observations of Sabbe et al. (1994), that dexmedetomidine induces a dose-dependent depression in the respiratory rate. It decreases respiratory rate with minimal effects on blood gases in dogs (Kuusela et al. 2001). In the animals of Group II, the pronounced decrease in RR may be explained by the action of fentanyl (Thurmon et al. 1999) along with dexmedetomidine. The action of midazolam might have added to the depression in RR in Group II. In Group III, respiratory rate might be depressed partly due to ketamine, which is known to have depressant effects on the respiratory system in a dose-dependent manner (Reich and Silvay 1989) and partly due to other drugs, as in Group II.

The decrease in rectal temperature recorded after the onset of effects in all groups might be attributed to a possible decrease in heat production due to sedation and decreased muscular activity. Activation of alpha-2C receptors by dexmedetomidine in the Groups I and II might have also contributed to hypothermia (Lemke 2007). In Group III, a direct depression of the thermoregulatory centre in the hypothalamus by ketamine may also be responsible for the decrease in temperature (Wright 1982).

Dexmedetomidine alone may have contrasting effects on blood pressure, since it non-selectively stimulates α_{2A} and α_{2B} adrenergic receptors (Ebert et al. 2000). Low doses produce hypotension due to α_{2A} stimulation and inhibition of norepinephrine release in the autonomic nervous system (MacMillan et al. 1996). High doses of dexmedetomidine may produce hypertension due to vasoconstriction resulting from stimulation of α_{2B} adrenoceptors in the smooth muscles of blood vessels (Lemke 2007). The initial increase in MAP in the animals of Group I may be due to high dose of dexmedetomidine. The decreased MAP in the later stages could be due to the predominant action of α_{2A} receptors. In the animals from Group II, the consistent decrease in MAP could be due to the action of dexmedetomidine with other pre-anaesthetics/anaesthetics (Sano et al. 2010). The increase in MAP in Group III may possibly be due to the cardio-stimulatory effects of ketamine. Ketamine induces an increase in cardiac output and heart rate and often causes significant increases in blood pressure (Serteyn et al. 1993; Zielmann et al. 1997). Thus, the combination of dexmedetomidine, midazolam, fentanyl and ketamine provided good stability in the blood pressure.

Onset of sedation time in Group I was almost similar to that reported in dogs after medetomidine administration (Amarpal et al. 1996). The rapid onset of the effects of medetomidine may be attributable to its lipophilic property (Amarpal et al.1996). Dexmedetomidine, an isomer of medetomidine was also thought to act in a similar manner to medetomidine. A decrease in the onset of sedation time and onset of recumbency time in Groups, II and III as compared to Group I may be attributable to the plausible synergistic interaction of midazolam, fentanyl and dexmedetomidine and to the lipophilic nature of ketamine producing a rapid effect (Lin, 2007). Reduction in onset of sedation time and onset of recumbency time after addition of pentazocine to medetomidine compared to medetomidine alone has been reported previously (Amarpal et al. 1996). Time to return of righting reflex in Group I conformed to the observations of Kuusela et al. (2001), who reported that dogs administered 20 μg/kg dexmedetomidine were laterally recumbent for at least up to 90 min. The slightly increased time to return of righting reflex, longer standing and complete recovery time in Groups II and III may plausibly have resulted from the pronounced sedation (Jacobson and Hartsfield 1993; Ko et al. 2000).

It is concluded that dexmedetomidine can be used safely with midazolam, fentanyl and ketamine to produce different levels of sedation, analgesia and anaesthesia as per the clinical demand in dogs without alarming changes in important physiological parameters.

REFERENCES

Amarpal, Pawde AM, Singh GR, Pratap K, Kumar N (1996): Clinical evaluation of medetomidine with or without pentazocine in atropinized dogs. Indian Journal of Animal Sciences 66, 219–222.

Bol CJJG, Vogelaar PW, Tang JP, Mandema JW (2000): Quantification of pharmacodynamic interactions between dexmedetomidine and midazolam in the rat. Journal of Pharmacology and Experimental Therapeutics 294, 347–355.

Chiu TH, Chen MJ, Yang YR, Yang J J, Tang FI (1995): Action of dexmedetomidine on rat coerulus neurons: intracellular recording in-vitro. European Journal of Pharmacology 285, 261–268.

Ebert TJ, Hall JE, Barney JE, Uhrich TD, Colinco MD (2000): The effects of increasing plasma concentration of dexmedetomidine in humans. Anesthesiology 93, 382–394.

Gross ME (2001): Tranquillizers, α_2-adrenergic agonists, and related agents. In: Adams HR (ed.): Veterinary Pharmacology and Therapeutics. 8thed. Iowa State University Press, Iowa. 268–298.

Haskins SC, Peiffer RL, Stowe CM (1975): A clinical comparison of CT1341, ketamine and xylazine in cats. American Journal of Veterinary Research 36, 1537–1543.

Hayashi Y, Rabin BC, Guo TZ, Maze M (1995): Role of pertussis toxin-sensitive G-proteins in the analgesic and anesthetic actions of α_2-adrenergic agonists in the rat. Anesthesiology 83, 816–822.

Hikasa Y, Ogasawara S, Takase K (1992): Alpha adrenoreceptor subtype involved in the emetic action in dogs. Journal of Pharmacology and Experimental Therapeutics 261, 746–754.

Jacobson JD, Hartsfield SM (1993): Cardiorespiratory effects of intravenous bolus administration and infusion of ketamine-midazolam in dogs. American Journal of Veterinary Research 54, 1710–1714.

Kending JJ, Savola MK, Woodly SJ, Maze M (1991): Alpha 2-adrenoceptors inhibit a nociceptive response in neonatal rat spinal cord. European Journal of Pharmacology 192, 293–300.

Klimscha W, Tong C, Eisenach JC (1997): Intrathecal α_2-adrenergic agonists stimulate acetylcholine and norepinephrine release from the spinal cord dorsal horn in sheep. An in vivo microdialysis study. Anesthesiology 87, 110–116.

Ko JCH, Fox SM, Mandsager RE (2000): Sedative and cardiorespiratory effects of medetomodine, medetomidine-butorphanol, and medetomidine-ketamine in dogs. Journal of American Veterinary Medical Association 216, 1578–1583.

Ko JCH, Fox SM, Mandsager RE (2001): Effects of preemptive atropine administration on the incidence of medetomidine induced bradycardia in dogs. Journal of American Veterinary Medical Association 218, 52–58.

Kuusela E (2004): Dexmedetomidine and levomedetomidine, the isomers of medetomidine, in dogs. [Dissertation.] University of Helsinki.

Kuusela E, Raekallio M, Anttila M, Flack I, Mosla S, Vainio O (2000): Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. Journal of Veterinary Pharmacology and Therapeutics 23, 15–20.

Kuusela E, Raekallio M, Vaisanen M, Mykkanen K, Ropponen H, Vainio O (2001): Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. American Journal of Veterinary Research 62, 1073–1080.

Lemke KA (2007): Anticholenergics and sedatives. In: Tranquilli WJ, Thurmon JC, Grimm KA (eds.): Lumb and Jones' Veterinary Anesthesia and Analgesia. 4th ed. Blackwell Publishing Ltd., Oxford.

Leppanen MK, Mckusick BC, Granholm, MM, Westerholm FC, Tulama R, Short CE (2006): Clinical efficacy and safety of dexmedetomidine and buprenorphine, butorphanol or diazepam for canine hip radiography. Journal of Small Animal Practice 47, 663–669.

Lin HC (2007): Dissociative anesthetics. In: Tranquilli WJ, Thurmon JC, Grimm KA (eds.): Lumb and Jones' Veterinary Anesthesia and Analgesia. 4th ed. Blackwell Publishing Ltd., Oxford. 301–353.

MacMillan LB, Hein L, Smith MS, Piascik MT, Limbird LE (1996): Central hypotensive effects of α_{2a}-adrenergic receptor subtype. Science 273, 801–803.

Posner LP, Burns P (2009): Injectable anesthetics. In: Riviere JE, Papich MG (eds.): Veterinary Pharmacology and Therapeutics. 9th ed. John Wiley and Sons, USA. 279–284.

Pypendop B, Verstegen J (1994): A comparison of sedative and analgesic effects of buprenorphine in combination with acepromazine, midazolam or medetomidine in dogs. Veterinary Anaesthesia and Analgesia 21: 15–20.

Reich DL, Silvay G (1989): Ketamine: an update on the first twenty-five years of clinical experience. Canadian Journal of Anesthesia 36, 186–197.

Sabbe MB, Penning JP, Ozaki GT, Yaksh TL (1994): Spinal and systemic action of the alpha-2 receptor agonist dexmedetomidine in dogs. Anesthesiology 80, 1057–1072.

Salmenpera MT, Szlam F, Hug Jr CC (1994): Anesthetic and hemodynamic interactions of dexmedetomidine and fentanyl in dogs. Anesthesiology 80, 837–846.

Sano H, Doi M, Yu S, Kurita T, Sato S (2010): Evaluation of the hypnotic and hemodynamic effects of dexmedetomidine on propofol-sedated swine. Experimental Animal 59, 199–205.

Savola MK, Woodley SJ, Maze M, Kendig JJ (1991): Isoflurane and an alpha 2-adrenoceptor agonist suppress nociceptive neurotransmission in neonatal rat spinal cord. Anesthesiology 75, 489–498.

Serteyn D, Coppens P, Jones R, Verstegen J, Philippart C, Lamy M (1993): Circulatory and respiratory effects of the combination medetomidine-ketamine in beagles. Journal of Veterinary Pharmacology Therapeutics 16, 199–206.

Shukry M, Miller JA (2010): Update on dexmedetomidine: use in nonintubated patients requiring sedation for surgical procedures. Therapeutic Clinical Risk Management 6, 111–121.

Thurmon JC, Tranquilli WJ, Benson GJ (eds.) (1999): Essentials of Small Animal Anaesthesia and Analgesia. 1st ed. Lippincott Williams and Wilkins, Baltimore. 134–136.

Tranquilli WJ, Gross ME, Thurmon JC, Benson GJ (1990): Evaluation of three midazolam-xylazine mixtures: preliminary trials in dogs. Veterinary Surgery 19, 168–172.

Wright M (1982): Pharmacological effects of ketamine and its uses in veterinary medicine. Journal of American Veterinary Medical Association 182, 1462–1471.

Zielmann S, Kazmaier S, Schull S, Weyland A (1997): S-(+)-ketamine and circulation. Anesthetist 46, S43–46.

Received: 2012–09–14
Accepted after corrections: 2013–03–08

Corresponding Author:

Amarpal, Division of Veterinary Surgery, Indian Veterinary Research Institute, Izatnagar-243122, India
Tel. +91 581 2302093, E-mail: amarpal@ivri.res.in