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Clonidine Premedication Before Etomidate-Halothane Anaesthesia in Dogs

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Abstract: The objective of this study was to evaluate 3 different doses of clonidine as a premedicant in dogs prior to etomidate-halothane anaesthesia. Six healthy dogs were anesthetized. Each dog received intravenously (i.v.) three different preanaesthetic protocols: CL6 (clonidine, 6 μg kg^{-1} i.v.), CL8 (clonidine, 8 μg kg^{-1} i.v.) or CL10 (clonidine, 10 μg kg^{-1} i.v.). Anesthesia was induced with etomidate (4±0.8 mg kg^{-1}) and maintained with halothane. The following variables were studied: Heart Rate (HR), Systolic Arterial Pressure (SAP), Diastolic Arterial Pressure (DAP), Mean Arterial Pressure (MAP), Respiratory Rate (RR), arterial oxygen saturation and end tidal CO_2. Arterial blood pH and arterial blood gas tension (PaO_2, $PaCO_2$) were measured during anaesthesia. Time to extubation, time to sternal recumbency and time to standing were also recorded. HR and RR decreased significantly during sedation in all treatments. CL6 and CL8 decreased significantly the arterial pressures after sedation but remained stable during the anaesthetic period. Respiratory variables during anaesthesia were statistically similar in all treatments. Halothane requirements were similar for CL6, CL8 and CL10. The combination of clonidine, etomidate and halothane appears to be effective for induction and maintenance of general anaesthesia in healthy dogs.

Key words: Clonidine, etomidate, halothane, anaesthesia, dogs, premedication

INTRODUCTION

Clonidine is a selective alpha-2 adrenergic agonist with some alpha-$_1$agonist activity and was first utilized as an antihypertensive drug in humans, but due to sedation and excessive mouth dryness (xerostomia) its use was restricted (Wallin and Frisk, 1981; Muzi *et al*., 1992). It has been considered useful as a sedative and analgesic agent. After intravenous (i.v.) injection in sheep, clonidine is widely distributed and has a rapid half-life absorption in Cerebrospinal Fluid (CSF) of 5.8 min and a terminal half-life of 95 min (Castro and Eisenach, 1989). A dose of 6 μg kg^{-1} i.v. clonidine decreased nociception in sheep for 120 min after thermal stimulation of the pinnae and for 90 min in a mechanically stimulated limb (Nolan *et al*., 1987). The analgesic effects of the alpha-$_2$ agonist drugs typically only last for half the duration of the sedation (Cullen, 1996). The major pharmacological effects of clonidine involve changes in blood pressure and heart rate, although the drug has a variety of other important actions (Hoffman and Lefkowitz, 1993). Others alpha-$_2$ agonist drugs, like xylazine, romifidine, dexmedetomidine or medetomidine have been used as a premedication in dogs before several protocols of general anaesthesia (Muir and Piper, 1977; England and Hammond, 1997; Gómez *et al*., 2006; Lerche and Muir, 2006). However, no studies were found on the influence of clonidine during general anaesthesia using etomidate-halothane in dogs.

Etomidate is a carboxylated imidazole anaesthetic agent. Is most commonly used in shocked or hemodynamically unstable patients; the ideal induction agent in emergency anaesthesia. This drug shows benefits features on the induction of general anaesthesia. Between their advantages are cited: hemodynamic stability, minimal respiratory depression, cerebral protection and rapid recuperation after a dose or continue infusion (Gooding and Corssen, 1977; Ledingham and Watt, 1983; Skarda *et al*., 1997). The minimal effect of the etomidate in the cardiovascular function is a principal advantage in humans (Criado *et al*., 1980) or in hypovolemic dogs (Pascoe *et al*., 1992). Following bolus administration for induction of anaesthesia, cardiac output and inotropy, systemic vascular resistance and arterial pressure are all well maintained (Clarke, 1997; Sprung *et al*., 2000). Etomidate inhibits the adrenal steroid synthesis pathway (Duthie *et al*., 1985). In the elective situation and among

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otherwise healthy patients who do not subsequently develop critical illness, adrenal suppression is relatively short and have not been associated with adverse outcomes, although there are limited data to confirm this (Vanacker *et al*., 1995). In dogs, a single bolus injection of etomidate reduces the adrenocorticol response to anaesthesia and surgery from 2-6 h after induction (Dodam *et al*., 1990). Etomidate reduce in 30% the intracranial pressure in patients with this condition increased (Dearden and McDowall, 1985) reducing the cerebral blood flow (34%) without alteration of the mean arterial pressure (Cold *et al*., 1985). Moreover, etomidate exhibits structural similarities to specific alpha-2 adrenoceptors agonists of the type such as dexmedetomzidine (Paris *et al*., 2003).

Halothane is a potent anaesthetic agent with properties that allow a smooth and rather rapid loss of consciousness that progress to anaesthesia (Marshall and Longnecker, 1993). Halothane causes hypotension by a dose-dependent reduction of arterial blood pressure. Two effects can cause this fact: The myocardium is depressed directly and cardiac output is decreased and the normal baroreceptor-mediated tachycardia in response to hypotension is obtunded. When anaesthesia is induced by inspiration of halothane at concentrations commonly necessary for surgical anaesthesia (0.8-1.2%), cardiac output is reduced by 20-50% from the level characteristic of the awake state (Marshall *et al*., 1969). Halothane causes a dose-related reduction in the ventilatory response to carbon dioxide (Knill and Gelb, 1978). The Minimum Alveolar Concentration (MAC) of halothane in dogs has been reported as 0.87 and 0.9% (Skarda *et al*., 1997; Padleford, 1999).

The objective of this research was to compare the clinical effects of clonidine in 3 different doses (6, 8 or 10 μg kg^{-1}) administered as premedicants before general anaesthesia with etomidate-halothane in dogs.

MATERIALS AND METHODS

The Ethics Committee of our faculty approved this study. Six dogs of undefined breed (2 males and 4 females) weighing 11.7±2.2 kg (mean±SD) were studied. All dogs were healthy based on clinical examination and haematological and serum biochemical analyses. Animals were trained and familiarized to handling, to the study room and to the personnel. The dogs were fasted for 12 h before each procedure. Three anaesthetic protocols were applied to every animal with a minimum of a 1 week interval between them. Each dog received intravenously (i.v.) the following preanaesthetics protocols: CL6-clonidine (Clonidin®: Cristália Chemical and Pharmacological Products Ltda, Brazil), 6 μg kg^{-1}; CL8-clonidine, 8 μg kg^{-1} and CL10-clonidine, 10 μg kg^{-1}. Before sedation, a 22-gauge catheter (Insyte, Becton, Dickinson Indústrias Cirúrgicas and Ltda) was placed in the cephalic vein and maintaining (10 mL kg h^{-1}) until the end of the experimentation period. Baseline data were collected before drug administration. All doses of clonidine were rapidly administered. During sedation, before etomidate administration, the quality of sedation was evaluated. Depth of sedation was rated by central effects produced by the doses of clonidine. The scale was: No sedative effects; mild sedation, reduced alertness and some response to acoustic stimuli; moderate sedation; drowsiness, head down, moderate palpebral reflex and partial eye rotation and marked sedation; lateral or sternal recumbency, no response to acoustic stimuli, head down, weak palpebral reflex and complete eye rotation.

In all anaesthetic protocols, 15 min after sedative administration, the anaesthesia was induced with i.v. etomidate (Etomidate®, Cristália Chemical and Pharmacological Products Ltda, Brazil) given slowly (4±0.8 mg kg^{-1}; mean±SD) until a suitable plane of anaesthesia for endotracheal intubation was achieved. A semi-closed circle rebreathing anaesthesia system was connected to the endotracheal tube. Anaesthesia was maintained with 0.8-1.2% halothane and 100% oxygenic. Halothane was administered at 1.0 MAC. One MAC was considered to be 0.9%. The dogs were placed in left lateral recumbency on a surgical table and volatile anaesthesia was maintained during 60 min.

Heart Rate (HR; beats min^{-1}), Mean Arterial Pressure (MAP; mmHg), Systolic Arterial Pressure (SAP; mmHg), Diastolic Arterial Pressure (DAP; mmHg), Respiratory Rate (RR; breaths min^{-1}), saturation of O_2 peripheral (SpO_2) and Rectal Temperature (RT; °C) were recorded prior to the administration of the three doses of clonidine, 5, 10 and 15 min following the administration of this sedative and at 10 min intervals during the anaesthetic period. Values of arterial blood pressure were measured non-invasively by an oscilometric method (RX-300[A] cardiac monitor; Transmai Equipamentos Médicos Hospitalares). The arterial blood pressure cuff was applied over the ulnar artery on the forearm. SpO_2 was measured using a sensor on the tongue. HR was measured using electrocardiography. RR was measured as the number of chest movements per minute and RT was measured with a digital thermometer.

After induction of sedation a catheter was placed in a femoral artery. An anaesthetic bottom was done on the internal region of the hind limb over the femoral artery and the catheter was inserted and washed with heparin after

each blood sample. During the anaesthesia, blood samples were collected from the arterial catheter for measurement of arterial pH (pHa), blood gas tensions (PaO_2, $PaCO_2$), bicarbonate (HCO_2) and base excess. Blood samples were collected anaerobically, syringes were stored in ice water and samples were analyzed within 30 m of collection. Samples were taken 15 m after sedation, at 30 and 60 m after induction of anaesthesia and measured by specific electrodes (ABL5 Radiometer, Copenhagen, Denmark).

During recovery, time in min to extubation (TE, the end of halothane administration to recovery of voluntary swallowing), time in min to Sternal Recumbency (SR) and time in min to standing (TS) were also recorded.

Statistical analysis: All data were analyzed using a statistical program. Dependent variables HR, SAP, DAP, MAP, RR, SpO_2, $EtCO_2$, pH and blood gas tension were analyzed using one-way Analysis of Variance (ANOVA) and the paired t-test was used to compare the means at different intervals to their base values within the group. Basal values of HR, SAP, DAP, MAP and RR were compared with the anaesthetic values within the same procedure. ANOVA was used to compare the variables TE, SR and TS between treatments. Sedation was analyzed by use of non-parametric Wilcoxon's Signed-rank test. In each analysis, differences were considered significant at values of $p<0.05$.

RESULTS

The degree of sedation induced by CL8 and CL10 was considered effective (score 4, lateral or sternal recumbency, no response to acoustic stimuli, head down, weak palpebral reflex and complete eye rotation). In the CL6 treatment sedation was recorded as moderate (score 3, drowsiness, head down and animal responded to external stimuli). No statistical differences were noted between treatments for TE, SR and TS (Table 1).

After premedication, HR and RR decreased in all treatments. First-degree atrioventricular blocks were noted with all doses. After CL6 and CL8, bradycardia began at 5 min and after CL10 at 15 min. The arterial pressures (SAP, DAP and MAP) did not show significant alterations after CL10 when compared to the basal value. Significant decreases in SAP, DAP and MAP occurred at 10 min until the end of the anaesthetic period in CL6 or CL8 treatments (Table 2).

The quality of induction of anaesthesia with etomidate was satisfactory and without excitement in all cases. There were no difficulties in endotracheal intubation. The mean dose (±SD) requirements of etomidate for induction were: CL6, 4.4±0.4 mg kg^{-1}; CL8, 4.0±0.4 mg kg^{-1} and CL10, 3.8±0.5 mg kg^{-1} (not statistical difference).

During anaesthesia, the HR decreased in all time points after induction in CL6 and CL8 and at 10-20 min in CL10. Significant decreases in SAP, DAP and MAP occurred at 10-60 min in CL6 and CL8 and at 40-60 min in the CL10 treatment. RR decreased significantly in all intervals in all groups after induction of anaesthesia until 60 min. Halothane requirements were similar for CL6, CL8 and CL10. During anaesthesia, there were no differences between the three groups for respiratory values (Table 3). Recovery times were statistically not different among the protocols (Table 4).

Table 1: Recovery times of six dogs anaesthetized with etomidate-halothane and premedicated with clonidine (CL6, 6 μg kg^{-1}; CL8, 8 μg kg^{-1}; CL10, 10 μg kg^{-1})

Treatments	Time to extubation (min)	Time to sternal recumbency (min)	Time to standing (min)
CL6	7.4±3.8	3.2±1.2	2.1±1.3
CL8	6.7±2.5	4.2±0.9	3.4±1.7
CL10	5.9±4.2	3.8±2.2	3.1±2.8

Data indicate mean±SD. Data are not statistically different ($p<0.05$) among treatments

Table 2: Cardiovascular values of 6 dogs anaesthetized with etomidate/halothane and premedicated with clonidine (CL6, 6 μg kg^{-1}; CL8, 8 μg kg^{-1}; CL10, 10 μg kg^{-1})

		Time (min)									
	Treatments	Basal	5 PS	10 PS	15 PS	10 PI	20 PI	30 PI	40 PI	50 PI	60 PI
HR	CL6	118±9	94±15*	88±17*	92±12*	85±20*	81±13*	88±12*	89±8*	91±15*	97±15
	CL8	108±17	91±13*	84±11*	84±12*	81±12*	70±6*	65±7*	68±9*	71±10*	78±12*
	CL10	102±15	85±18	78±13	72±13*	68±11*	71±8*	79±17	80±17	83±18	81±13
SAP	CL6	138±15	122±14	124±18*	112±7*	101±11*	88±13*	86±15*	82±16*	87±14*	87±14*
	CL8	135±14	118±10	106±19*	108±9*	90±12*	90±15*	96±22*	99±15*	101±15*	100±16*
	CL10	133±18	128±20	123±20	116±19	108±27	102±34	104±25	94±23	94±24	96±22
DAP	CL6	102±14	82±13	79±19*	75±15*	64±6*	57±17*	58±12*	50±8*	52±8*	55±8*
	CL8	91±23	78±18	65±13*	75±14*	53±12*	57±13*	57±17*	60±19*	65±16*	66±18*
	CL10	94±19	87±25	83±21	77±18	75±33	61±28	69±32	55±27	60±29	61±25
MAP	CL6	113±14	93±18	98±21*	90±14*	81±9*	70±10*	71±12*	65±10*	67±9*	72±8*
	CL8	105±8	88±13	80±19*	89±12*	68±12*	72±14*	74±20*	77±17*	82±14*	80±15*
	CL10	110±16	105±22	99±22	94±19	93±34	75±27	84±26	76±25	76±26	76±23

Data indicate mean±SD. PS, Post Sedation values; PI, post anaesthetic induction values; HR, Heart Rate (beats min^{-1}); SAP, Systolic Arterial Pressure (mmHg); DAP, Diastolic Arterial Pressure (mmHg); MAP, Mean Arterial Pressure (mmHg), *Significantly different from baseline values ($p<0.05$)

Table 3: Respiratory variables of 6 dogs anaesthetized with etomidate/halothane and premedicated with clonidine (CL6, 6 μg kg^{-1}; CL8, 8 μg kg^{-1}; CL10, 10 μg kg^{-1})

			Time (min)								
	Treatments	Basal	5 PS	10 PS	15 PS	10 PI	20 PI	30 PI	40 PI	50 PI	60 PI
RR	CL6	34±7	26±9*	24±6*	20±3*	13±5*	11±5*	13±7*	14±5*	17±6*	17±4*
	CL8	27±6	21±4	20±6*	20±10*	14±6*	13±4*	15±5*	16±4*	18±3*	17±5*
	CL10	29±8	23±7	21±5*	19±7*	15±6*	13±6*	13±5*	14±4*	15±5*	16±3*
SpO_2	CL6	ND	ND	ND	ND	98±1.0	97±0.8	98±0.6	98±1.0	99±0.8	99±0.4
	CL8	ND	ND	ND	ND	98±0.8	96±1.9	96±1.3	97±1.9	98±1.2	98±1.5
	CL10	ND	ND	ND	ND	97±3.1	96±2.6	97±2.3	97±1.8	98±1.5	98±1.6
$EtCO_2$	CL6	ND	ND	ND	ND	50±3	51±3.1	52±4.9	50±3	49±1.7	49±2.1
	CL8	ND	ND	ND	ND	46±4.2	46±3.6	47±7	46±6	47±7	46±5.8
	CL10	ND	ND	ND	ND	50±6.5	47±8	48±7.8	47±10	47±12	47±14.9

Data indicate mean±SD. PS, Post Sedation values; PI, post anaesthetic induction values. RR, Respiratory Rate (breaths min^{-1}); SpO2, saturation of O_2 peripheral; $EtCO_2$, ND, Not Determined. *Significantly different from baseline values ($p<0.05$)

Table 4: Arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), pH, bicarbonate, base excess and temperature during anaesthesia, in 6 dogs anesthetized with clonidine (CL6, 6 μg kg^{-1}; CL8, 8 μg kg^{-1}; CL10, 10 μg kg^{-1})

		Time (min)		
Variable	Treatments	15	30	60
PaO_2 (mmHg)	CL6	203±87	301±103	287±116
	CL8	332±74	386±107	351±82
	CL10	238±86	372±89	397±84
$PaCO_2$ (mmHg)	CL6	45±15	52±21	48±9
	CL8	55±10	44±10	47±6
	CL10	67±15	72±12	69±11
pH	CL6	7.32±0.02	7.22±0.01	7.27±0.0.3
	CL8	7.22±0.01	7.36±0.06	7.34±0.02
	CL10	7.23±0.02	7.29±0.04	7.25±0.03
Bicarbonate (mmol L^{-1})	CL6	20±1.5	21±2.4	19±2.3
	CL8	21±3.4	20±4.4	19±5.1
	CL10	21±3.7	20±4.9	20±4.7
Base excess (mmol L^{-1})	CL6	-6.8±3.8	-8.5±3.7	-7.8±3.1
	CL8	-9±5.7	-5.8±6.5	-5.5±3.8
	CL10	-8.5±6.3	-9.7±6.7	-8.7±5.5
Temperature (°C)	CL6	37.3±0.2	37.2±0.2	37.2±0.1
	CL8	37.5±0.3	37.4±0.2	37.3±0.2
	CL10	38.4±0.4	38.2±0.3	38.1±0.3

Data indicate mean±SD. *Significantly different from baseline values ($p<0.05$)

DISCUSSION

The election of preanaesthetics medication is important in any general anaesthesia protocol in small animals. Sadly, the majority of the drugs used in the veterinary medicine induce cardio-respiratory alterations that can be important in weak patients. Based in previous studies involving other species, we selected three doses of clonidine to analyse its sedative, analgesic and systemic effects in dogs. After i.v. clonidine, the sedative effect was superior and more rapid with CL10 and was exhibited within 2 min. Ataxia, muscular relaxation, sternal or lateral recumbency; lowering of the head and closing of the eyelids were seen. These signs have been described in dogs sedated with other alpha-2 adrenergic agonists (Vainio, 1991; Kuusela *et al*., 2001; Gómez *et al*., 2006).

Alpha-2 agonists applied intravenously in sheep produce biphasic changes in heart rate and arterial pressure, initially enhancement and increased heart rate and arterial pressure and then, decrease of these signals (Celly *et al*., 1997). In our study, marked reduction of HR was observed during sedation but there were no changes in arterial pressure in CL10. At low doses, alpha-2 agonists stimulate the central sympathetic preganglionar neurons in spinal cord and in high doses stimulate peripheral adrenoceptors (Hall and Clarke, 1991). It is proved that in central action alpha-2 agonists produce hypotension whereas the stimulation of peripheral alpha-2 adrenergic receptors in the smooth vascular musculature results in vasoconstriction (Maze and Tranquilli, 1991).

Sedation with alpha-2 agonists results in respiratory depression secondary to the central nervous system depression produced by alpha-2 adrenoceptors stimulation (Sinclair, 2003). RR was reduced in this study in dogs in all protocols during sedation. This is in agreement with the dose-related depression of RR in dexmedetomidine-sedated dogs previously reported (Kuusela *et al*., 2001). Other significant fact is that the degree and significance of respiratory depression produced by any alpha-2 agonist will be increased when

the agonist is given along with other sedatives. Decreased respiratory rate, increased arterial carbon dioxide tension (Cullen and Reynoldson, 1993; Thurmon *et al*., 1994) hypoxemia and cyanosis (Cullen and Reynoldson, 1993; Vainio, 1991) have been reported in dogs premedicated with medetomidine and induced with propofol.

Intravenous administration of etomidate produced excitement-free induction of anaesthesia in all dogs and without intubation difficulties, similar to other reports of anaesthesia in alpha-2 agonist premedicated dogs (Vainio, 1991, Cullen and Reynoldson, 1993, Gómez *et al*., 2006). In this study, CL6, CL8 and CL10 required no significant different doses of etomidate for anaesthetic induction. However, CL10 reduced the required induction dose of etomidate compared with CL6.

After the administration of etomidate the HR remained bellow of the basal values but stable until the end of the experimental period. Etomidate causes minimal changes in the cardiovascular function in dogs (Criado *et al*., 1980; Pascoe *et al*., 1992) but halothane causes hypotension by a dose-dependent reduction. In our study, only CL10 did not cause decrease in SAP, DAP and MAP during anaesthesia. Probably, this fact occurred with the higher dose of clonidine due to the induced peripheral vasoconstriction, thus preventing the hypotensive effect (Eisenach *et al*., 1987). Another factor could be that the etomidate acts as an agonist at alpha-2B-receptors, which appears *in vivo* primarily as an alpha-2B-receptor-mediated increase in blood pressure. This effect of etomidate may contribute to the cardiovascular stability of patients after induction of anaesthesia with etomidate (Paris *et al*., 2003).

A progressive decrease in RR was observed in all treatments. Similar results were obtained with etomidate infusion after medetomidine-premedication in dogs causing decrease in respiratory function but minimal changes in hemodynamic values (Ko *et al*., 1994). Etomidate causes a minimal respiratory depression, cerebral protection and rapid recuperation after a dose or continued infusion (Gooding and Corssen, 1977; Ledingham and Watt, 1983; Skarda *et al*., 1997). Halothane causes a dose-related reduction in the ventilatory response to carbon dioxide (Gibbons *et al*., 1977; Knill and Gelb, 1978). In our study, there were no differences in respiratory variables ($EtCO_2$, SpO_2, $PaCO_2$, PaO_2) during anaesthesia.

After general anaesthesia (etomidate/halothane) the dogs woke up quietly and without any excitation in all treatments. All dogs were extubated within±10 min after the end of anaesthesia. Other inhalant anaesthetics, like desflurane or sevoflurane induce a faster recovery from anaesthesia due to its low solubility in the blood (Clarke, 1999; Gómez *et al*., 2006). The blood gas partition coefficient for desflurane (0.49±0.03; mean±SD) is smallest, followed by sevoflurane (0.62±0.04), isoflurane (1.27±0.06) and halothane (2.46±0.09) in humans (Yasuda *et al*., 1991). A higher blood gas partition coefficient and slow changes in the alveolar anaesthetic concentration induce a more long-lasting recovery from anaesthesia (Yasuda *et al*., 1991).

Etomidate induce minimal cardiovascular effects (Pascoe *et al*., 1992). Increased doses of clonidine in this study enhanced the sedation and analgesia and lowered the duration and potential severity of negative cardiovascular side effects. However, we can not affirm that our dose is high in dogs (CL10) because there are no studies in the literature to compare. While hypotension may occur, sedative doses of clonidine typically did not alter or raise the blood pressure due to the effect on peripheral alpha-2 adrenoreceptors (Eisenach *et al*., 1987; Sinclair, 2003).

CONCLUSION

In conclusion, the studied doses of clonidine (6, 8 and 10 μg kg^{-1}) in combination with etomidate and halothane seem to be effective for induction and maintenance of general anaesthesia in healthy dogs. It provided a satisfactory preanaesthetic management and reduced the induction dose of etomidate. During the anaesthetic period the cardiorespiratory variables remained in satisfactory levels.

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