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RESEARCH ARTICLE

Cardiovascular, Antinociceptive and Sedative Effects of Medetomidine Infusion in Sevoflurane Anesthesia in Puppies

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ABSTRACT

The objective of this study was to determine the effect of a constant rate infusion of medetomidine in the cortical brain activity and hemodynamic parameters in sevoflurane anesthetized puppies. Six puppies of the age of two weeks old were included in the study and were anaesthetized three times with sevoflurane. On the first anesthesia, each dog's minimum alveolar concentration (MAC) for sevoflurane was determined by the use of the tail clamp method. On the second anesthesia (sevoflurane), the puppies were anesthetized at each of five multiples of their individual's MAC, 0.75, 1, 1.25, 1.5 and 1.75 MAC, and bispectral index and cardiorespiratory parameters were registered. On the third anesthesia (sevoflurane+ medetomidine), puppies were anesthetized at each of five multiples of their individual's MAC, and medetomidine (5 µg/kg+2µg/kg/h) was administered. Mild cardiovascular depression was observed in sevoflurane+medetomidine in comparison with sevoflurane. Cortical and antinociceptive effects were not observed with medetomidine infusion although a mature EEG response to noxious stimulation would not have developed in puppies. Central alpha-2 adrenoreceptors would be immature in puppies during the first two weeks of life, and for this reason, medetomidine would not produce sedative and analgesic effects in young puppies. More studies have to be performed to support this statement.

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INTRODUCTION

Medetomidine is an α_2-agonist with a great affinity for the adrenergic receptors, which shows sedative, analgesic and relaxing muscular properties (Kaartinen *et al*., 2010). Medetomidine, such as other α_2-agonists, induces dose-dependent cardiovascular changes like bradycardia, atrioventricular block or hypotension (Grint *et al*., 2010). Medetomidine is used in dogs widely with different protocols. Recent studies have demonstrated the utility of an infusion of medetomidine in adult dogs (Kaartinen *et al*., 2010) but there are no references about its use in puppies.

Clinical parameters, such as hemodynamic parameters, are used usually to establish the anesthetic plane. However, these may be influenced by factors that are not related with the anesthetic depth. For this reason, the use of monitors to set the anesthetic depth objectively has increased in the last decade. One of these monitors is the Bispectral Index (BIS). Bispectral index is a parameter derived from the EEG that indicates the degree of cortical brain hypnosis (Greene *et al*. 2002). It is a dimensionless number from 0 to 100 and it is indirectly related with anesthetic depth, so if the BIS value is near to 100 the patient is awake and if the BIS value is near to 0, the anesthetic plane is very deep and shows absence of brain electrical activity. There are studies that support the use of bispectral index in dogs (Greene *et al.* 2003; Morgaz *et al*., 2009).

In the balanced anesthesia, small amounts of different drugs are combined to obtain a correct anesthetic plane. This strategy has the advantage of reducing the adverse effects of large doses of drugs which may be necessary if each drug is used alone (Ortega and Cruz, 2011). The use of sedatives, analgesics and locoregional techniques reduce the concentrations of inhalant anesthetics and therefore decrease its adverse dose-dependent effects, so the morbidity and mortality of patients are lowered and

the anesthetics conditions are very safe (Ilkiw, 1999). For this reason, the use of sedatives or opiods in young animals anesthetized with inhalational agents would provide greater security in the anesthesia of these patients.

The objective of this study was to determine the effect of a constant rate infusion (CRI) of medetomidine in the cortical brain activity and hemodynamic parameters in sevoflurane anesthetized puppies.

MATERIALS AND METHODS

Animals: The experimental protocol was approved by the Ethical Committee of the University of Cordoba. Five 2 weeks old beagles (three females and two males) were used in the study. The weight of the puppies was 2.69±0.93 kg. Food was not withdrawn before of the beginning of the study to avoid hypoglycemia.

Instrumentation and study design: Each animal was anesthetized three times, with a washout period of 7 days between anesthesia. In the first anesthesia, the individual MAC of sevoflurane was measured in each animal (Morgaz *et al*., 2009). On the second anesthesia (S protocol), the animals were anesthetized with sevoflurane at five different multiples (0.75, 1, 1.25, 1.5 and 1.75 MAC) of their individual's MAC. On the third anesthesia (SM protocol), the puppies were anesthetized with five different multiples MAC of sevoflurane and medetomidine (bolus of 5 µg/kg of medetomidine intravenously and a CRI of 2µg/kg/h). The infusion of medetomidine started when the instrumentation has finished. The application order of the each MAC was random for each animal by means of a Latin square.

In S and SM protocols, the anesthetic induction was carried out with sevoflurane in oxygen administered by mask. After that, animals were intubated and intermittent positive pressure ventilated (IPPV) (7900 SmartVent Ventilator, GE Healthcare, GE, Finland) was started in all the patients to maintain normocapnia ($EtCO_2$ between 35 and 45 mmHg) and a constant end tidal of sevoflurane. Dogs were connected to a closed circle rebreathing system and sevoflurane in oxygen 100% was administered with a gas fresh flow of 50 mL/kg/min. Catheters were placed in the metatarsian artery and in the cephalic vein and the monitoring was performed. At each of the five MAC of sevoflurane, after fifteen minutes of calibration the experiment was started. Later, the values of BIS and the other variables of the study were recorded during two periods differentiated by a painful stimulus. The first period was named *pre-stimulus period* and it was 20 minutes before of the painful stimulus was applied, in which the parameters were recorded every 5 min. The second period was named *post- stimulus period* and it lasted for six min. One minute during painful stimulus and five minutes after the stimulus. During this period the values were recorded every thirty seconds. The painful stimulus consisted on clamping the tail with an atraumatic forceps during 1 min. At the end of the post-stimulus period, a blood arterial sample was collected for gas analysis (Gasometer Ciba-Corning, Mod. 850 Chiron Diagnostics, Madrid, Spain).

In the two periods, heart rate (HR), respiratory rate (RR), pulsi-oxymetry (SpO_2), oesophageal probe to measure temperature (T^a), end-tidal carbon dioxide ($EtCO_2$), direct systolic (SAP), diastolic (DAP) and mean (MAP) arterial blood pressure, BIS (A-2000 version 3.4, Aspect Medical System Inc, Norwood, MA, USA) and end-tidal of sevoflurane (EtSev) (Datex-Ohmeda Multifunctional Anesthesia Monitor, GE Healthcare, GE, Finland) were measured. The position of BIS was frontotemporal on Fp2 (primary lead), F4 (secondary lead) and T4 (ground lead).

Statistical analyses: The statistical program used was SPSS 15.0 for Windows. Heart rate, RR, SAP, DAP, MAP, $EtCO_2$, EtSev, BIS values and blood gas parameters were analyzed. Each value was compared before and after the stimulus was applied between S and SM protocols using an ANOVA for repeated measures. Pearson correlation was performed in S and SM to evaluate the relationship between BIS values and hemodynamic parameters, and in the same way, between BIS values and sevoflurane MAC. Values of $P<0.05$ were considered significant in ANOVA, whereas for Pearson correlation were $P<0.01$. Results are reported as mean±SD.

RESULTS

The mean MAC of sevoflurane for the group of puppies was 2.14±0.22. Three animals in S protocol and two in SM protocol were not evaluated at 0.75 MAC during the post-stimulus period by the presence of spontaneous movements of the head, hind limbs or forelimbs with the clamping.

The values of cardiorespiratory parameters and BIS are shown in Table 1 and 2. The HR was higher in S than in SM at all MACs, as well as the MAP in the pre-stimulus period. Moreover, during the post-stimulus period only at 1 and 1.25MAC there were significant differences between both protocols, with higher values in S than in SM. The values of SAP were higher significantly in S than in SM, except at 0.75MAC in post-stimulus period, at which not significant differences were found.

No significant changes in BIS values were found between both protocols. BIS was only significantly different between protocols at 1.25 MAC during pre-stimulus period and 1.75MAC during post-stimulus period. The results of Pearson correlation are showed in Table 3. There were no significant differences in blood gas parameters.

DISCUSSION

Medetomidine, like others α2-agonists, produces important cardiovascular changes like biphasic effect of arterial blood pressure, a decrease of HR and cardiac output (Grint *et al*., 2010). Greene *et al.* (2003) described in dogs anesthetized with isoflurane that the administration of 8 µg/kg of medetomidine reduced the values of HR in comparison to the control group, although significant differences there were not detected to the blood pressures. Our results agreed partially with them, since the values of HR were higher in S group than in SM group, but the blood pressure values in SM were significantly lower than S group, although not significant

Table 1: Cardiorespiratory parameters and BIS values in the *pre-stimulus* period in puppies receiving Sevoflurane (S) and Sevoflurane followed by constant rate infusion of medetomidine (SM) (2 μg/kg/h). Data are represented as mean±SD

Variable	Protocol	0,75 MAC	1MAC	1,25MAC	1,5MAC	1,75MAC
Heart rate (beats/min)	S	137±16[a]	137±6[a]	129±12[a]	141±10[a]	132±10[a]
	SM	99±12[a]	99±11[a]	96±10[a]	97±5[a]	95.5±5[a]
Respiratory rate (breaths/min)	S	19±2	18±3	18±3	18±3	18±3
	SM	21±2	21±2	21±2	22±2	21±2
Mean arterial pressure (mmHg)	S	85.1±14.3[a]	79.4±21.7[a]	75.8±7.3[a]	71.6±13.1[a]	57.0±7.8
	SM	69.3±4.8[a]	63.9±4.8[a]	60.6±9.3[a]	58.1±4.8[a]	53.3±9.1
Systolic arterial pressure (mmHg)	S	109.1±20.1[a]	107.7±15.4[a]	99.1±12.9[a]	97.8±15.3[a]	82.9±11.8[a]
	SM	96.8±7.1[a]	89.9±7.1[a]	86.7±10.5[a]	79.2±6.2[a]	71.9 ±13.1[a]
Diastolic arterial pressure (mmHg)	S	66.8±14.5[a]	62.6±10.3[a]	58.9±7.8[a]	54.3±8.4	43.0±5.7
	SM	55.8±3.3[a]	51.2±4.2[a]	50.7±6.1[a]	48.2±5.1	44.9±7.1
End tidal dioxide carbon (mmHg)	S	36.0±5.5[a]	38.5±3.1[a]	34.7±3.9[a]	38.3±6.5[a]	40.4±3.5
	SM	40.4±1.4[a]	39.7±2.3[a]	40.3±3.5[a]	41.7±4.4[a]	41.9±3.7
Bispectral index	S	59.6±13.2	50.0±6.2	49.5±14.8	44.3±9.2	40.8±4.8
	SM	61.9±7.3	51.4±10.1	44.4±6.5	44.3±7.8	40.9±9.2

[a]Significantly different (P< 0.05) from the MAC multiple during the same measurement period between S and SM protocol.

Table 2: Cardiorespiratory parameters and BIS values in the *post-stimulus* period in puppies receiving Sevoflurane (S) and Sevoflurane followed by constant rate infusion of medetomidine (SM) (2 μg/kg/h). Data are represented as mean±SD

Variable	Protocol	0,75 MAC	1MAC	1,25MAC	1,5MAC	1,75MAC
Heart rate (beats/min)	S	130±10	146±9	119±32	132±13	131±6
	SM	116±11	107±7	101±8	101±5	96±4
Respiratory rate (breaths/min)	S	25±4	20±7	17±2	19±7	18±3
	SM	24±3	21±2	21±3	21±2	22±3
Mean arterial pressure (mmHg)	S	77.3±12.1	87.2±16.1[a]	87.1±9.9[a]	70.6±9.2	59.3±12.8
	SM	81.4±8.3	73.2±12.1[a]	66.7±6.5[a]	64.6±8.3	56.2±9.8
Systolic arterial pressure (mmHg)	S	99.7±16.2	110.2±16.9[a]	112.5±13.3[a]	94.5±10.7[a]	81.7±14.6[a]
	SM	109.6±7.9	99.4±13.6[a]	91.9±7.7[a]	85.7±8.4[a]	74.4±15.6[a]
Diastolic arterial pressure (mmHg)	S	63.0±11.1	69.8±13.3[a]	70.7±9.1[a]	54.2±6.1	46.3±7.3
	SM	66.8±8.3	60.1±11.3[a]	54.1±7.1[a]	53.2±7.8	47.2±7.8
End tidal of carbon dioxide (mmHg)	S	27.5±1.9 [a]	33.5±5.3	37.2±6.7	39.9±6.1	41.2±4.1
	SM	38.0±2.5	39.2±2.2	39.4±3.8	41.1±3.5	40.3±2.2
Bispectral index	S	76.7±2.1	62.5±15.2	47.1±11.1	42.7±10.9	39.2±5.9
	SM	74.1±5.4	63.8±12.2	43.7±6.7	43.1±7.7	46.0±9.9

[a]Significantly different (P< 0.05) from the MAC multiple during the same measurement period between S and SM protocol.

Table 3: Pearson correlations between Bispectral Index and hemodynamic parameters and MAC in both protocols

Protocol	Analysis	HR	MAP	SAP	DAP	MAC
S	Pearson correlation	0.113[a]	0.160[a]	0.106	0.229	-0.532[a]
	P	0.034	0.005	0.068	0.060	0.001
SM	Pearson correlation	0.383[a]	0.435[a]	0.437[a]	0.409[a]	-0.513[a]
	P	0.001	0.001	0.001	0.001	0.001

[a]Significantly (P< 0.01) different from the MAC multiple during the same measurement period between Sevoflurane (S) and medetomidine (SM) protocol.

differences were found at elevated MAC. Therefore, the values of HR in the study of Greene *et al.* (2003) were lower than our values, especially at low MACs. This could be caused by the age of the patients, since they used adult dogs whereas we employed puppies. The cardiac output in puppies is determined by the HR specially, and for this reason HR is higher in puppies than in adults (Holden, 2007).

A painful stimulus causes an activation of sympathetic nervous system (SNS), liberation of endogenous catecholamines and significant adverse effects as tachycardia, tachypnea or hypertension (Lemke and Creighton, 2010). Although we did not measure the release of catecholamines in blood levels, we observed that HR and blood pressures increased significantly after the painful stimulus until 1.5MAC in both protocols. Moreover, the animals were not synchronized with the ventilator after the painful stimulus at low MACs of sevoflurane in the SM group. So, we could conclude that an infusion of medetomidine of 2.0μg/kg/h does not avoid the sympathetic stimulation of the painful stimulus in puppies and therefore it lacks of analgesic effects. One hypothesis would be that central α2 adrenoceptors are immature in the puppies in the first weeks of life and for this reason medetomidine would not produce sedative and analgesic effects.

We used BIS to detect the sedative effect of medetomidine since it is used in humane medicine to determine the depth of anesthesia, and also BIS has been evaluated in dogs with different anesthetics as isoflurane and sevoflurane (Greene *et al*., 2003). In our study, we did not found significant differences in BIS values between S and SM groups and even, BIS values at 1.75MAC in SM group were higher than S group. This observation disagreed with the conclusions of a study in which the authors observed that medetomidine reduced BIS values at 0.8, 1 and 1.5MAC of isoflurane in dogs (Greene *et al*., 2002). However, in that study a high variability of BIS values were registered at low MACs. The absence of differences in BIS values between our protocols could be due to that CRI of medetomidine was insufficient. The most common CRI of medetomidine in dogs is 0.5-1 μg/kg/h (Gómez-Villamandos *et al*., 2008) but there are not references about the rate infusion or pharmacokinetics of medetomidine in puppies. The infusion used in this study is based on dexmedetomidine dose in children. This drug is the active enantiomer of the medetomidine and it is responsible of its sedative and analgesic effects. Dexmedetomidine has double potency than medetomidine (Kuusela *et al*., 2000). The normal dose of dexmedetomidine in neonates is 1 μg/kg/h (Klamt *et al*., 2010) so for this reason, we doubled the CRI of medetomidine in puppies to 2 μg/kg/h. We observed the

typical hemodynamic changes of α2-agonists in SM group so we consider that our CRI of medetomidine should be enough to join to α_{2A}-adrenoreceptors and cause sedative effects, and moreover, our rate was higher than adult normal rates. In any case, further investigation on medetomidine pharmacokinetics and pharmacodynamics should be performed in puppies to confirm it. In this sense, it would be possible that the medetomidine actions on the CNS depend on the age and when the neurosystem is fully developed.

The EEG changes with the age and for this reason the EEG of the puppies is different than adult dogs (Petersen *et al*., 1964). In a recent study in which one week old kittens sedated with medetomidine and butorphanol, the authors observed an important evolution of EEG during the weeks later to birth (Lewis *et al*., 2011). Since BIS is a number derived to EEG and therefore the BIS values would be different depending on the age. In humans, BIS is useful to determine the anesthetic plane in children but the values are age-dependent (Lamas *et al*., 2009). The influence of the age on the BIS has not been evaluated in dogs. In our study, BIS values were correlated significantly with the anesthetic plane, so, we believe that the differences observed between both treatments for the BIS but should be due to the anesthetic protocol used, although future investigations are needed to determine the influence of age on BIS in dogs.

Sevoflurane may produce patters of epileptiform activity in children (Constant *et al*. 2005). This alteration has been associated with excitatory action on *loecus coeruleus* by sevoflurane (Yasui *et al.,* 2007), being this nucleous the target place of α2 agonist. We did not observe patters of epileptiform activity on the EEG in our study, but if the differences in BIS in our study were associated to sevoflurane, the values of BIS in S group should be different than SM group because of the patters of epileptiform activity would have been blocked in SM group by the medetomidine inhibition on *loecus coeruleus*.

Conclusion: We concluded that a constant rate infusion of medetomidine of 2µg/kg/min does not provide antinociceptive and sedative effects in puppies anesthetized with sevoflurane, although it does not produce important hemodynamic alterations. However, further research is needed to clarify certain issues.

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