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Echocardiographic evaluation of the cardiovascular effects of medetomidine, acepromazine and their combination in healthy dogs

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ABSTRACT

The aim of this study was to compare the cardiovascular effects of medetomidine, acepromazine and their combination administered intravenously in healthy dogs. Ten dogs were included in this study and randomly assigned to the three different sedative protocols: medetomidine (2 μg/kg, protocol M), acepromazine (20 μg/kg, protocol A) and acepromazine followed by medetomidine with the same doses as above (protocol AM), in three different times. In all subjects before (Tbase) and 15 (T15), 50 (T50) and 80 (T80) minutes after the administration of the drugs, the following non-invasive measurements were obtained: blood pressure with oscillometric method, ECG, and echocardiography. Blood pressure and echocardiography evidenced decrease in left ventricular afterload secondary to acepromazine and an increase in right ventricular afterload due to medetomidine. The combination of the two drugs mitigated the effects expected by the single drugs used alone, and prevented the onset of atrioventricular blocks, such as seen in protocol M. The three protocols were eligible for sedation and premedication in healthy dogs. Moreover they had little impact on the echocardiographic variables evaluated in this study.

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1. Introduction

Medetomidine and acepromazine are the main sedative drugs used in small animal patients (Paddleford, 2000). Medetomidine is a highly selective α_2-adrenoceptor agonist, which produces dose dependent sedation, hypnosis and analgesia (Murrell and Hellebrekers, 2005). Its mechanism of action is the stimulation of α_2 pre-synaptic type A adrenoceptors, providing inhibition of the release of norepinephrine (Scheinin and MacDonald, 1989). This mechanism, at the level of the "locus coeruleus", results in sedation. Peripherally, medetomidine stimulates post- and extrasynaptic α_2 type B adrenoceptors located in the smooth muscle of peripheral arterioles, leading to vasoconstriction and increase in blood pressure (Pypendop and Verstegen, 1998; Dugdale, 2010). The main cardiovascular effects of medetomidine in dogs are the initial increase in systemic afterload and the subsequent bradycardia, sinus arrests and atrioventricular (AV) blocks (Pypendop and Verstegen, 1998; Sinclair, 2003). Bradyarrhythmias and conduction disturbances are likely due to the increase in the vagal tone resulting from the stimulation of baroreceptors and to the decrease in sympathetic outflow from the central nervous system (Sinclair, 2003). Acepromazine is a drug that exerts its sedative effects by the blockade of dopamine receptors in the central nervous system. The main cardiovascular effects of acepromazine are mediated by the block of the peripheral α_1-adrenoceptors at level of the peripheral arterioles, which provides vasodilatation, decrease in vascular resistance and compensatory increase in heart rate (Paddleford, 2000; Monteiro et al., 2007). Preservation of the hemodynamic condition is important for patients undergoing sedation before surgery and/or for diagnostic procedures that are aimed to investigate the cardiovascular function (e.g. echocardiography). Based on the opposite effects on afterload of acepromazine and medetomidine, the hypothesis of this study was that combining low doses of the two drugs, we could achieve in dogs a synergistic sedative effect with a better hemodynamic condition compared to those provided by the two drugs used alone. In order to test this hypothesis, sedation and non-invasive right and left ventricular afterload were assessed in dogs treated with acepromazine, medetomidine and their combination.

2. Materials and methods

2.1. Animals

Ten unrelated female dogs, aged between 8 and 60 months (median = 19.8 months), and weighing between 15 and 35 kg (median = 22.7 kg) were enrolled in this study after the written owner's informed consent was obtained. All dogs were scheduled for a reproductive monitoring that required at least three weakly

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echographic evaluations and were considered healthy based on physical examination and blood analysis. All dogs underwent also a complete echocardiographic evaluation in order to exclude any pre-existing heart disease.

2.2. Study design

All dogs received three different sedative protocols with a week washout period between each of them: 2 μg/kg of medetomidine (Domitor®, Pfizer) (protocol M), 20 μg/kg of acepromazine (Preqillant 1%, Fatro Spa) (protocol A), 20 μg/kg of acepromazine and 15 min later, 2 μg/kg of medetomidine (protocol AM). Drugs were administered intravenously via an over-the-needle catheter, placed into a cephalic vein 30 min before the beginning of the study. Dogs were conducted in the examination room 15 min before starting the study, to acclimatize them to the environment and personnel. During the entire study, dogs were placed on an examination table allowing to assume the spontaneous recumbency between the echocardiographic examinations that were performed with the dog standing with the aid of an assistant.

Assessment of the sedative (sedation score) and cardiovascular (M-mode, two-dimensional and Doppler echocardiography, electrocardiography and blood pressure measurements) effects was performed 20 min before (Tbase) and 15 (T15), 50 (T50) and 80 (T80) minutes after the administration of the drugs (T0). For the AM protocol, T0 was considered the time of the second drug (medetomidine) administration. Sedation was always assessed before the echocardiographic examination.

2.3. Echocardiography

Echocardiograms were performed always by the same operator (VS) blinded to the study protocol, according to the American Society of Echocardiography standards, in standing dogs (Chetboul et al., 2005) with an ultrasound unit (LOGIQ 400 PRO Series, GE Medical Systems) equipped with a 2–5 MHz phased-array transducer. Examination was performed through the right parasternal window in short axis for M-mode and pulmonary artery Doppler measurements, and in long axis for two-dimensional measurements. The aortic Doppler variables were obtained through the left apical window in long axis. M-mode variables included the left ventricular internal dimension in systole (LVID), which was also indexed (I/LVID) according to a standard formula (Cornell et al., 2004), and the thickness of the left ventricular posterior wall in systole (LVPW). These parameters were also used to calculate the end-systolic left ventricular wall stress (Wstr) as follows:

$$\mathrm{Wstr} = (\mathrm{SAP} \times \mathrm{LVID})/[(4 \times \mathrm{LVPW}) \times (1 + \mathrm{LVPW}/\mathrm{LVID})]$$

where SAP represents the systolic arterial pressure obtained with the oscillometric technique. Parameters that required ECG synchronization (left ventricular internal dimension in diastole, fraction of shortening, and ejection fraction by Teicholz formula) were not included in the study since this feature was not available in the ultrasound unit. Two-dimensional long axis variables, indexed for the body surface area included: end-diastolic and end-systolic left ventricular volumes (EDVI and ESVI, respectively) obtained by the area-length formula and stroke index (SI = EDVI−ESVI); ejection fraction was calculated with the Dodge formula (EF-Dodge). The frames selected from the video-loops for off-line measurements of end-systole and end-diastole in long axis were, respectively, the last frame preceding the first mitral opening and the first frame where coaptation of mitral leaflets followed the second mitral opening. Doppler measurements included spectral analysis of the pulmonary artery flow in pulsed-wave mode, to obtain the peak velocity (Peak P), and calculate the following systolic time intervals: ejection time (ET P), acceleration time (AT P) and acceleration/ejection time ratio (AT/ET P) (Schober and Baade, 2006; Serres et al., 2007). To minimize the effect of the heart rate (HR) on systolic time intervals, they were also indexed for the HR (e.g. ET P_c) as previously described (Schober and Baade, 2006). After changing the echocardiographic window from the right parasternal to the left apical, aortic flow was interrogated by pulsed-wave Doppler to obtain the peak velocity (Peak Ao) and the ejection time (ET Ao), the latter being also corrected for HR. Each measurement was taken over three consecutive cardiac cycles and then averaged and used for the final data analysis.

2.4. Blood pressure measurement

Systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were measured (SC 6002XL, Siemens, Denver, MA, USA) simultaneously with echocardiography, at each study time (Tbase, T15, T50 and T80) considering the mean of five consecutive measurements. A cuff with a height of 40% of the tail base circumference was positioned over the base of the tail and remained in place all over the study. The averaged value of SAP was used for calculating Wstr.

2.5. Electrocardiography

Single lead continuous ECG was obtained via the same monitor used for blood pressure measurements. Heart rate was measured, simoultaneously with echocardiography, at each study time (Tbase, T15, T50 and T80) considering the mean of five consecutive measurements. It was also recorded during the echocardiographic measurement of SI in order to calculate the cardiac index (CI) by the following formula: CI = HR × SI. Electrocardiogram was continuously observed for twenty minutes at each study time to detect the onset of arrhythmia and for its scoring. Arrhythmic events were scored taking into account two parameters: times of appearance during the 20 min of observation (1 = one time; 2 = two or more times), and duration (1 = < 10 s; 2 = > 10 < 30 s; 3 = >30 s). Based on the sum of the scores of the two parameters, arrhythmia was defined as rare (1–2 points), frequent (3) and very frequent (4–5).

2.6. Sedation score

Sedation was assessed at each study time according to a sedation score previously published (Smith et al., 2001). General appearance of the patient, interactive behaviour, restrainability, and response to the hand clap, were evaluated, with positive and/or negative scores. The total sedation score was obtained as the sum of the scores of the single parameters (Table 1).

2.7. Statistical analysis

Statistical analysis was performed with a commercially available software (MedCalc version 9.2.0.1. Regged-rG). For all data, normal distribution was tested with Levene's test and the mean (±standard deviation) or the median (range) were calculated. A one way analysis of variance (ANOVA) for repeated measures followed by the Student–Newman–Keuls test was used for within and between groups comparisons for parametric data. Non parametric data (sedation score) were analyzed with the Kruskal–Wallis test for between and within groups comparisons. Multiple linear stepwise regression analysis was performed with most left echocardiographic parameters (LVIDI, ESVI, EF-Dodge, Peak Ao, ETAo, ETAoc, Wstr, SI, CI) and SAP and MAP as dependent variables, for each protocol. The coefficient of variation was calculated in order to test the intraobserver day-to-day repeatability (Moise et al., 1985), for the following echocardiographic variables: LVID, ESVI,

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