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Original Article

Lidocaine administered at a continuous rate infusion does not impair left ventricular systolic and diastolic function of healthy rabbits sedated with midazolam

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ABSTRACT

Lidocaine is a versatile drug that not only provides local anesthesia, but also reduces anesthetic requirements of other agents and has antiarrhythmic, pro-kinetic, anti-inflammatory, antiendotoxemic and antioxidant effects. As it is a drug commonly used in critically ill patients, its safety from the cardiovascular system should be ensured. The aim of this study was to determine the effects of a continuous rate infusion (CRI) of lidocaine on left ventricular systolic and diastolic function of healthy rabbits sedated with midazolam by use of transthoracic echocardiography.

Ten New Zealand healthy rabbits were sedated with intramuscular midazolam (1 mg/kg) and enrolled in two experimental treatments (control or lidocaine). The control treatment (CT) comprised an intravenous bolus of 0.9% sodium chloride (0.05 mL/kg) followed by CRI at 5 mL/h, whereas the lidocaine treatment (LT) comprised a bolus of 2% lidocaine without epinephrine at 1 mg/kg followed by CRI at 50 μg/kg/minute. Echocardiographic and hemodynamic variables were studied. Variables were recorded at baseline (TB) and 20, 40 and 60 minutes following start of CRI (T20, T40 and T60, respectively). No differences were found between treatments. The results of this study demonstrate that a continuous rate infusion of lidocaine at 50 μg/kg/minute does not impair echocardiographic indices of left ventricular systolic and diastolic function of healthy rabbits sedated with midazolam.

Introduction

Lidocaine is a versatile drug that not only provides local anesthesia, but also reduces anesthetic requirements of other agents and has antiarrhythmic, pro-kinetic, anti-inflammatory, antiendotoxemic and antioxidant effects (Alves et al., 2014; Feary, Mama, Wagner, & Thomasy, 2005; Mikawa et al., 1997; Mudge, 2007; Muir, Wiese, & March, 2003; Peiró et al., 2010; Robertson, Sanchez, Merritt, & Doherty, 2005; Valverde, Doherty, Hernández, & Davies, 2004; (Pypendop and Ilkiw, 2005). A number of studies have demonstrated that continuous rate infusion (CRI) of lidocaine reduce the requirement of inhalation anesthetics during orthopedic and soft tissue surgical procedures in humans and animals (Valverde et al., 2004; Ortega, Cruz, 2011; Weinberg et al., 2017). In addition, Bakan et al., 2015 have associated its use to lesser postoperative analgesic requirements.

The properties of lidocaine render it an interesting drug for critical patients, although its effects on hemodynamics are yet to be elucidated. Studies addressing this issue tend to disagree regarding the cardiovascular effects of lidocaine, and the effects of a CRI on heart function are rarely studied. Binnion, Murtagh, Pollock, & Fletcher, 1969 reported negative inotropic effects with the use of high doses of lidocaine in dogs. One study in rabbits showed a decrease on cardiac output following an intravenous (IV) bolus of lidocaine at 1 mg/kg (Wiktorowska, Owczarek, & Orszulak-Michalak, 1999). David et al., 2007, when studying the in vitro effects of lidocaine on rat myocardium, demonstrated negative inotropic and lusitropic effects. Takada, Dohi, Akamatsu and Suzuki,

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2007 demonstrated a negative chronotropic effect of lidocaine in dogs, although these authors did not observe a decrease on cardiac output.

Among the methods currently used for hemodynamic assessment in veterinary medicine, transthoracic echocardiography is an interesting non-invasive alternative, seeing as it allows real-time observation of the cardiac cycle, thereby improving the comprehension of the interaction between drugs and myocardial dynamics (Hanai et al., 1996; Jugdutt, Menon, Kumar, & Idikio, 2002; Marques et al., 2018; Saponaro et al., 2013). To date, only a few studies have investigated the effects of a CRI of lidocaine on echocardiographic variables related to left ventricular systolic and diastolic function in animals. Understanding the interaction between lidocaine and the cardiac cycle is crucial to its safe use in clinical practice, in animals and humans.

Therefore, the objective of this study was to assess, through transthoracic echocardiography, the effects of a CRI of lidocaine on left ventricular systolic and diastolic function of healthy rabbits sedated with midazolam. The hypothesis tested in the study was that, compared to a CRI of 0.9% NaCl, lidocaine at 50 μg/kg/minute would not produce clinically relevant changes on echocardiographic variables reflecting left ventricular systolic and diastolic function of healthy rabbits.

Materials and methods

Animals

Ten unneutered New Zealand white rabbits (four males and six females) aged 9 months and weighing 3.2 ± 0.3 kg were enrolled in the study. Subjects were deemed healthy based on physical examination, echocardiography and electrocardiography. During the participation in the study, animals were kept in individual stalls, where they received commercial feed twice daily, vegetables once daily and water ad libitum. The study was approved by the local Ethics Committee for Animal Usage under protocol No. 00437-2017.

Study design

Prior to each procedure, subjects were fasted for two hours. The order of participation was determined by a random number generated using Microsoft® Office Excel[1]. To achieve proper immobility of the rabbits during echocardiographic examinations, midazolam[2] was administered intramuscularly at 1 mg/kg. Following 10 minutes of midazolam administration, animals were blindfolded and restrained in a rabbit restraint box for venous and arterial catheterization. For this purpose, lidocaine at 2% (0.05 mL) was injected perivascularly at the central auricular artery and the marginal ear vein to allow insertion of a 24-gauge catheter, respectively for invasive arterial pressure monitoring and intravenous treatment administration. Both catheters were coupled to a *pro re nata* (PRN) adaptor and infused with heparin solution.

The same animals participated in both treatments with a minimum washout period of 7 days. Experimental treatments comprised: CT, control treatment using 0.9% sodium chloride at 5 mL/h; and LT, lidocaine[3] treatment using 2% epinephrine-free lidocaine at previous bolus of 1 mg/kg followed by CRI of 50 μg/kg/minute, diluted in 0.9% sodium chloride to a total of 5 mL/h. The intravenous bolus in CT was administered at the same volume calculated for LT for each subject. All infusions were given by use of a syringe pump[4].

Physiological variables were recorded before treatment administration (TB) and 20, 40 and 60 minutes following start of CRI (T20, T40 and T60, respectively). Data collection was performed by a professional who was unaware of the treatment. Heart rate (HR) was obtained through an electrocardiographic recording generated by the echocardiograph[5]. Systolic, diastolic and mean arterial pressure (SAP, DAP and MAP, respectively) were obtained directly from a multiparametric monitor[6] with the transducer zeroed at heart level. Peripheral vascular resistance index (PVRI) was calculated as PVRI = (MAP/DCI) × 80, where DCI is the Doppler cardiac index (L/min/m2) = (DEI [mL/m2] × HR [beats/min])/1,000 and DEI is the Doppler ejection index = (VTI × Aao)/BSA; VTI is the velocity-time integral; Aao is the aortic area measured at the two-dimensional view of the left ventricle in its short axis at the aortic plane measured during the early diastole; BSA is the body surface area calculated as BSA = (9.9 × [body weight {in grams}]$^{2/3}$)/10,000 (Zehnder, Hawkins, Trestrail, Holt, & Kent, 2012).

To minimize the effects of stress on physiologic parameters, subjects were handled by the same individuals and analyses were performed in the same room with animals blindfolded during data collection.

Echocardiographic examination

For optimal imaging during echocardiographic examinations, the left and right parasternal areas of all subjects were clipped. Assessments were always performed by a single examiner using an echocardiograph[5] with multifrequency transducer (4-11 MHz) and real-time recording of electrocardiography. The exams were performed within 6-8 minutes. Data were stored for further analysis and calculations.

Left ventricular echocardiographic variables were obtained in M-mode at the right parasternal window with the rabbit in right lateral recumbency. The left ventricular end-diastolic diameter (LVEDD) was measured from two-dimensional images in the parasternal long-axis view in the chordal plane, using the R wave as reference. The same was performed for the left ventricular end-systolic diameter (LVESD) using the T wave (Boon, 2011). These measurements were then used to calculate left ventricular end-diastolic and end-systolic volume (LVEDV and LVESV, respectively) (Teicholz, Kreulen, Herman, & Gorlin, 1976).

Subjects were then positioned in left lateral recumbency for the four-chamber apical view at the left parasternal window. Peak velocity of early left ventricular filling (E wave) and atrial contraction (A wave) were measured. The aortic flow was then visualized by pulsed wave Doppler at the five-chamber view for velocity-time integral (VTI) assessment. The isovolumic relaxation time (IVRT) was obtained with the cursor placed between the output of the left ventricle and the transmitral flow and recorded from the end of transaortic flow to the beginning of the E wave (Boon, 2011).

The mitral annular tissue motion was assessed using pulse Doppler at the four-chamber apical view with sample volume placed on the lateral border of the mitral annulus. Two negative peak tissue velocities were obtained: the peak early left ventricular filling (E′ wave) and atrial contraction (A′ wave). In addition, a positive peak obtained during the systolic phase was determined as the S′ wave.

Measured variables were further used for calculation of the ejection fraction (EF), shortening fraction (SF) was calculated as SF = [LVED – LVESD] / LVED) × 100); Doppler cardiac index (DCI); Doppler ejection index (DEI), E:A and E′:A′ ratio (Boon, 2011).

Statistical Analysis

Variables were first tested for normal distribution using Shapiro-Wilk test and further compared through ANOVA for repeated measures followed by Tukey post-hoc test. Analyses were performed using a computer software[7]. Differences were considered significant when $p<0.05$.

[1] Microsoft® Office Excel.
[2] Dormire® 15mg/3mL, Cristália LTDA, São Paulo, Brazil.
[3] Xylestesin® 2% without epinephrine, Cristália LTDA, São Paulo, Brazil.
[4] Syringe pump BSS 200-Biosensor, São Paulo, Brazil.
[5] MyLabTM 70 X Vision, Esaote®.
[6] Digicare LW9X, Boynton Beach, Florida, USA.
[7] GraphPad Prism 6.01, GraphPad Software Inc., California, USA.

Results

Results from the variables assessed in this study are shown on Tables 1 and 2. Variables, HR, SAP, DAP, MAP, PVRI, DCI, EF, S′ wave and IVRT did not differ between groups or among time points. Although no differences were found between treatments, DEI significantly increased at T20, T40 and T60 (16%, 22% and 20%, respectively) compared to TB. A significant increase (15%) was observed at T60 for LVEDV and LVESV compared to TB, only in LT. However, despite the increase in LT, groups did not differ according to Tukey test.

Transmitral flow assessment showed superposition of E and A waves in 30% (12/40) of the analyses in CT and in 32.5% (13/40) of cases in LT. Neither treatment showed E:A ratio<1. Tissue Doppler examination showed superposition of E′ and A′ waves in 2.5% (1/40) of cases in CT and 12.5% (4/40) in LT. All subjects in CT and LT showed E′:A′ ratio>1.

Discussion

The effects of a CRI of lidocaine on left ventricular systolic and diastolic function of lagomorphs is scarcely studied in laboratory animal clinical care. The results of this study demonstrated that lidocaine at 50 μg/kg/minute did not induce clinically significant changes on left ventricular function in healthy rabbits. These findings render lidocaine an interesting and safe option for use in these species, given that the infusion rate of 50 μg/kg/minute is widely used in most domestic species.

Table 1
Echocardiographic and hemodynamic variables (mean ± standard deviation) of healthy rabbits sedated with midazolam and undergoing constant rate infusion of 0,9% NaCl (CT, n=10) or lidocaine (LT, n=10) during 60 minutes of evaluation.

Variable	Time (minutes) Treatment	Baseline	20	40	60
HR (beats/minute)	CT	218 ± 25	203 ± 24	199 ± 20	204 ± 22
	LT	230 ± 22	213 ± 25	200 ± 12	200 ± 15
MAP (mmHg)	CT	80 ± 7	85 ± 10	85 ± 7	89 ± 10
	LT	82 ± 6	85 ± 7	80 ± 6	86 ± 9
LVEDD (mm)	CT	13.9 ± 1.6	13.7 ± 1.2	14.0 ± 0.9	13.6 ± 1.7
	LT	12.7 ± 0.7	13.6 ± 1.0	13.8 ±1.1	14.6 ± 0.8 [a]
LVESD (mm)	CT	9.7 ± 0.9	9.6 ± 0.8	10.0 ± 1.1	9.8 ± 1.4
	LT	9.0 ± 0.6	9.7 ± 0.6	9.7 ± 0.9	10.3 ± 0.7 [a]
SF (%)	CT	30 ± 5	30 ± 4	29 ± 5	28 ± 5
	LT	29 ± 3	28 ± 3	29 ± 2	29 ± 3
EF (%)	CT	61 ± 7	61 ± 6	60 ± 7	59 ± 7
	LT	60 ± 5	59 ± 4	61 ± 3	60 ± 4
S′ wave (m/s)	CT	0.10 ± 0.01	0.07 ± 0.01	0.08 ± 0.02	0.08 ± 0.01
	LT	0.09 ± 0.03	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.01
DEI (mL/beat × m^2)	CT	15.14 ± 2.29	14.24 ± 1.74	14.92 ± 2.76	15.19 ± 2.50
	LT	14.12 ± 3.03	16.43 ± 3.46[a]	17.19 ± 1.83[a]	16.93 ± 2.41[a]
DCI (L/minute × m^2)	CT	3.31 ± 0.63	2.87 ± 0.29	3.00 ± 0.77	3.08 ± 0.45
	LT	3.22 ± 0.61	3.50 ± 0.93	3.45 ± 0.47	3.40 ± 0.64
PVRI (dyne × s/cm^5 × m^2)	CT	2005 ± 394	2378 ± 334	2423 ± 692	2370 ± 454
	LT	2041 ± 368	2000 ± 579	1883 ± 286	2020 ± 368

[a] Significantly different from baseline according to Tukey test (p<0.05). HR, heart rate; MAP, mean arterial pressure; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; SF, shortening fraction; EF, ejection fraction; S′ wave, peak myocardial velocity during systole; DEI, Doppler ejection index; DCI, Doppler cardiac index; PVRI, peripheral vascular resistance index. 95% Confidence interval.

Table 2
Echocardiographic variables (mean ± standard deviation) used to assess left ventricular diastolic function of healthy rabbits sedated with midazolam and undergoing constant rate infusion of 0,9% NaCl (CT, n=10) or lidocaine (LT, n=10) during 60 minutes of evaluation.

Variable	Time (minutes) Treatment	Baseline	20	40	60
E wave (m/s)	CT	0.64 ± 0.12	0.59 ± 0.16	0.65 ± 0.13	0.67 ± 0.13
	LT	0.67 ± 0.10	0.58 ± 0.12	0.67 ± 0.08	0.67 ± 0.11
E′ wave (m/s)	CT	0.10 ± 0.01	0.09 ± 0.01	0.09 ± 0.01	0.09 ± 0.01
	LT	0.09 ± 0.02	0.09 ± 0.02	0.08 ± 0.01[a]	0.09 ± 0.02
E′:A′ ratio	CT	2.18 ± 0.70	1.96 ± 0.46	1.92 ± 0.41	1.74 ± 0.39
	LT	1.64 ± 0.45	1.72 ± 0.69	1.79 ± 0.43	1.92 ± 0.56
IVRT (ms)	CT	46 ± 2	45 ± 4	45 ± 3	46 ± 4
	LT	48 ± 3	45 ± 4	46 ± 2	45 ± 4

[a] Significantly different from CT according to Tukey test (p <0.05). E wave, peak velocity of early left ventricular filling; E′ wave, early diastolic velocity of annulus motion for the lateral wall of the mitral annulus; IVRT, isovolumic relaxation time; E′:A′ ratio, E′ wave-to-A wave ratio. E′:A′ was not measured in 2.5% (1/40) of times in CT and 12.5% (5/40) of times in LT due to wave superposition.

The choice of a rabbit model of study was based on cardiovascular system similarities in comparison to humans (Silva et al., 2011). However, given the natural behavior of rabbits, echocardiographic examination under solely physical restraint was not possible. In addition, when trying to perform echocardiography on awake rabbits, a longer period of time was needed for HR to stabilize due to sympathetic stimulation during restraint, which would impair cardiovascular examinations. Therefore, midazolam at 1 mg/kg was included in the experimental protocol according to Silva et al., 2011 who reported adequate sedation with minimal influence on HR and echocardiographic variables of healthy rabbits. The addition of midazolam was crucial to allow optimal imaging, and thus more reliable results.

Transthoracic echocardiography is not only interesting for being a non-invasive technique, but also for providing real-time images of the heart function, thereby allowing precise analysis of the events that follow each cardiac cycle. While other authors used invasive methods to monitor hemodynamic function following lidocaine administration (Wiktorowska et al., 1999), this study used echocardiography to assess the effects of lidocaine on systolic and diastolic function of healthy rabbits. Similarly to a study by Kim, Choi, Kim, & Hyun, 2015 lidocaine at 50 μg/kg/minute did not produce important changes on systolic and diastolic function of dogs along 60 minutes of infusion.

The pharmacodynamic characteristics of intravenously administered lidocaine were scarcely addressed in rabbits. Thus, the choice of the infusion rate was based on previous studies in dogs (Schnellbacher et al., 2013), in which 50 μg/kg/minute was shown to be a safe choice in the clinical scenario. This infusion rate did not produce significant changes on HR along 60 minutes of evaluation, which corroborates the results of other studies that did not report clinically relevant changes on HR in rabbits and dogs (Kim et al., 2015; Schnellbacher et al., 2013).

Left ventricular systolic function was assessed through the analysis of EF, SF and LVESD, which is a feasible method to approach cardiovascular function in rabbits, according to Silva et al., 2011. While EF and SF did not differ among treatments or time points, LVESD and LVEDD showed a slight increase over time, which only reached statistical significance at T60 (15%). However, from a hemodynamic standpoint, these results are not clinically relevant, given that the increase was discrete and all variables remained within acceptable limits for the species (Giannico et al., 2015). Therefore, the results show that lidocaine did not influence left ventricular systolic function, according to

these methods.

With regard to DEI, there was no difference between the two treatment protocols, although a slight increase could be seen at all time points compared to baseline. These results are in contrast with reports in other species (Araújo et al., 2014; Pypendop, Ilkiw, 2005; Wiktorowska et al., 1999), in which DEI showed a slight decrease over time during lidocaine infusion. Given that DEI can be influenced by preload, afterload and myocardial contractility (Pypendop and Ilkiw, 2005), variables such as LVEDD and PVRI can be used to assess preload and afterload, respectively. In this study, none of these variables showed clinically significant changes over time. Similarly, systolic function remained stable at all times, as demonstrated by EF, SF and LVESD.

Seeing as HR and DEI remained stable throughout the study, no important changes were found on DCI in both treatment groups. These findings diverge from another study by Wiktorowska et al., 1999, in which cardiac index showed a decrease following IV administration of lidocaine at 1 mg/kg in rabbits. However, the decreased was regarded as minimal by the authors. Arterial blood pressure also remained stable in this study, which could be explained by the stability seen on DCI and PVRI, given that arterial pressure is directly influenced by cardiac output and peripheral vascular resistance (Muir, 2017).

The maximum mitral annular myocardial velocity (S′ wave) was used to assess the function of longitudinal fibers on the left ventricle. Most conditions that lead to systolic dysfunction affect primarily longitudinal fibers before radial and circumferential fibers. Therefore, assessing the function of longitudinal fibers is crucial to an early diagnosis of systolic disfunction (Ballo et al., 2007). In this study, the S′ wave did not show important changes with the use of lidocaine compared to the control treatment, thus demonstrating that lidocaine did not influence cardiac inotropism at the studied infusion rate.

Transmitral flow, as well as variables related to tissue motion and IVRT, was used to investigate the effects of lidocaine on left ventricular diastolic function. Diastolic dysfunction can precede systolic dysfunction (Bonagura, Schober, 2009), which renders these variables crucial to the comprehension of left ventricular function as a whole. In this study, the higher HR of lagomorphs compared to humans cause a superposition of waves, and the A wave was indistinguishable in 30 and 32.5% of the examinations in CT and LT, respectively. Since tissue Doppler analysis is less influenced by HR, waves were fused only in 2.5 and 12.5% of the cases in CT and LT, respectively. The incidence of superposition was greatest at TB, which impairs comparison of the results to baseline measurements. However, during pulsed wave spectral tissue Doppler, none of the subjects showed E′:A′ ratio<1, thereby demonstrating normal pattern of relaxation (Boon, 2011). A few studies demonstrated E′ wave reduction with the aggravation of diastolic dysfunction (Koyama, Ray-Sequin, Davidoff, & Falk, 2002). In this study, although a slight reduction could be seen on E′ wave in LT at T40, the analysis of other variables indicated that this was not clinically relevant. In addition, IVRT did not differ among treatments or time measurements, thus demonstrating that there was no impairment of left ventricular diastolic function with the use of lidocaine. The pulsed wave spectral tissue Doppler was crucial to assess diastolic function, since it was less influenced by HR.

According to the literature, there are conflicting results regarding the effects of lidocaine on the cardiac function and hemodynamics. In vitro and in vivo studies with high doses have demonstrated reduced cardiac output, systemic blood pressure and IRVP (Binnion et al., 1969; David et al., 2007; Wiktorowska et al., 1999). Wilson, Soei, Bezstarosti, Lamers, & Verdouw, 1993 postulated that high doses (400 μg.mL-1) of lidocaine reduce the oxygen supply to the myocardium, without changing its oxygen consumption, and reduces calcium uptake by the sarcoplasmic reticulum, thereby decreasing concentrations of calcium available for contraction. However, this article points out that the deleterious effects on contractility occur only in high doses. Our results, on the other hand, corroborate with Grossman, Cooper and Frieden, 1969 who did not observe significant changes on HR, cardiac index, and systemic arterial blood pressure in humans with severe cardiac involvement and subjected to lidocaine infusion. Therefore, therapeutic doses such as those used by Grossman et al., 1969, Burton, Mathew, & Armstrong, 1976 and in the present study do not provide significant changes in cardiac function.

This study has a few limitations worth mentioning. The use of healthy animals limits the applicability of the results in patients with cardiovascular conditions, mainly those with left ventricular systolic or diastolic dysfunction, in which discrete variations can lead to clinically relevant changes. The behavior of rabbits warranted the use of midazolam to provide sedation and immobility, which could also influence the results. Furthermore, the small sample size and the short period of evaluation might have been insufficient to elicit relevant changes in cardiovascular variables, mainly those related to the accumulation of the drug. The infusion rate used in this study was based on other domestic species, but might have been insufficient to demonstrate cardiovascular changes in lagomorphs. Finally, the use of more advanced echocardiographic techniques, such as speckle tracking, would provide more accurate information on myocardial deformities, thus improving comprehension of the interactions between lidocaine and the heart.

Conclusions

The results of this study demonstrate that a continuous rate infusion of lidocaine at 50 μg/kg/minute does not influence echocardiographic indices of left ventricular systolic and diastolic function of healthy rabbits sedated with midazolam. Thus, under the experimental conditions used in this study, lidocaine is safe from a cardiovascular standpoint.

Conflict of interest statement

None of the authors has any financial or personal relationships that could inappropriately influence or bias the content of the paper.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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