EVALUATION OF KETAMINE - DROPERIDOL ANESTHESIA IN DOGS

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Abstract

The main objective of this study was to observe the influence of anesthesia combined with ketamine and droperidol, compared both in bolus administration and in continuous intravenous infusion, following the effects on cardiac and respiratory function. The experiment was performed on 16 clinically healthy dogs that had previously been pre-anesthetized with acepromazine intramuscularly at a dose of 0.5 mg / kg. The dogs were divided into two groups (A and B). The group A (n = 8) was given the combination ketamine (8 mg / kg) / droperidol (1 mg / kg), intravenously, in a bolus, through the cephalic vein, in a time interval of more than 30 seconds. Group B (n = 8) was given the same combination and through the same vein, but in continuous infusion over a period of approximately 20 minutes. Ketamine and droperidol were mixed in the same syringe shortly before bolus administration. The study was repeated in 6 dogs, using only acepromazine, 0.5 mg / kg, to evaluate the influence of the preanesthetic on the results obtained in the 2 groups A (bolus) and B (infusion). The results of the study showed that the ketamine / droperidol combination should be used with caution in dogs pre-anesthetized with acepromazine, but the effect of anesthesia combined with ketamine and droperidol is better than that of anesthesia only with ketamine.

Key words: anesthesia, ketamine, droperidol

INTRODUCTION

Anesthesia is a common practice in the daily work of a veterinary office for pets. Studies show that there is a very wide range of anesthetic protocols, probably because practitioners are in constant search of a "magic", balanced formula that does not induce side effects and endanger the health of the animal (Farnworth M.J., et al., 2014; Gates M.C., et al., 2020). Unfortunately, there is no single drug that has the characteristics of an ideal anesthetic agent, so we must carefully choose that combination of anesthetics that will help us achieve the desired effects.

Choosing the appropriate protocol for the surgical situation will often allow for lower doses, thus limiting the detrimental influence of these substances on the body's physiological functions. Moreover, many of these combinations of anesthetics work synergistically and thus can correct some of the side effects, which manifest themselves in their separate administration.

With characteristics such as rapid onset and cardio stimulatory properties, the combination of ketamine - droperidol may be ideal for inducing general anesthesia in dogs. Although heart rate and blood pressure may be elevated in non-anesthetized patients, ketamine causes decreases in blood pressure and cardiac output in people anesthetized with halothane (Kurdi M.S. et al., 2014).

Continuous infusion of ketamine and midazolam has been used successfully in human medicine for various investigations (Baillie, R., et al., 1989; Miller A.C. et al., 2011). Intravenous infusion of anesthetic agents for the maintenance of general anesthesia is considered to avoid environmental pollution associated with inhaled anesthetics. Continuous infusion compared to intermittent, injectable administration may result in reduced total need for anesthetic agents, improved intraoperative conditions, and reduced recovery time (Miller A.C. et al., 2011).

In our study, we aimed to evaluate the effectiveness of the anesthesia of the combination of ketamine and droperidol, compared in bolus administration and in continuous intravenous infusion.

MATERIAL AND METHOD

The experiment was performed on 16 dogs of common breed, without owner (9 females and 7 males), with an average weight of 18.1 ± 1.2 kg (M ± DS), clinically healthy. Prior to the experiment, they underwent a rigorous pre-anesthesia physical examination to assess their health. The animals were stopped feeding 12 hours before the study, but the water was ad libitum.

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Pre-anesthesia was performed with acepromazine at a dose of 0.5 mg/kg, intramuscularly, 15 minutes before the general anesthetic combination. Each dog had a branula (i.v. cannula, Novalon 1.25 IN, 20 GA, Becton, Dickinson Co, Sandy) inserted into the cephalic vein. The analysis of blood gases (PaO2 and PaCO2) and pH was performed computerized using the AVL Compact analyzer. The bicarbonate plasma concentration (HCO3-, meq / l) and the basic excess (EB, meq / l) were also calculated.

A non-invasive automatic device (Digital Electronic Blood Pressure Monitor, Model FC 150 D, Tokyo, Japan) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP). Heart rate (beats/minute) was determined by applying a precordial stethoscope. The body temperature was maintained between 37 - 38^0C with the help of Gelpack® (plastic bags with special thermal gel for raising or lowering the body temperature).

The dogs were divided into two groups A and B. The group A (n = 8) was given the combination ketamine (8 mg/kg) - droperidol (1 mg/kg), intravenously, in a bolus, through the cephalic vein a time interval of more than 30 seconds. Group B (n = 8) was administered the same combination through the same vein, but in continuous infusion over a period of approximately 20 minutes. Ketamine and droperidol were mixed in the same syringe shortly before bolus administration. For infusion, the ketamine-droperidol combination was diluted with 0.9% saline shortly before injection.

The study was repeated in 6 dogs, using only the preanesthetic, respectively acepromazine - 0.5 mg / kg, to evaluate the influence of the preanesthetic on the results obtained in the 2 groups A (bolus) and B (infusion).

After performing the first measurements, to obtain the basic data, the ketamine-droperidol combination was administered through the 2 procedures: bolus and infusion. Heart and respiratory rate, SBP (systolic blood pressure), DBP (diastolic blood pressure) and MBP (mean blood pressure) were recorded at minutes 1, 5, 10, 20, 30, 40, 50 and 60 of anesthesia. During the infusion, measurements were also made 5 minutes (-10 min.) and 10 minutes (-5 min.) After administration of the ketamine-droperidol combination. Blood samples were collected at 15, 30, 45, and 60 minutes.

Statistical analysis

Data analysis was performed with the ANOVA test for repeated measurements. When there were significant differences, the comparison of the averages was done using the Tukey test. The Student (t) test was used to compare the averages between the 2 groups: A (bolus) and B (infusion), relative to baseline values to ensure that the study conditions were similar for both groups. A significant level $p < 0.05$ was used.

Ethical implications

The study was conducted in accordance with national and international legal regulations on animal welfare, identification, control and elimination of factors causing physiological and behavioral disorders: Directive EC86 / 609 EU.

RESULTS

Body weight and mean time from induction of anesthesia with acepromazine 0.5 mg/kc to completion of instrumentation and baseline (comparison) were not significantly different between the 2 groups (A and B).

The average time interval from induction to collection of all data necessary to establish baseline values for dogs in the 2 groups A (bolus) and B (infusion) was 63 ± 11 minutes and 52 ± 15 minutes, respectively.

Body temperature decreased significantly over time in dogs in the bolus group (A). The difference in body temperature was significant between the two groups of dogs. Body temperature in group A dogs was on average 1^0C higher than group B temperature.

The hemodynamic effects of bolus and infusion ketamine-droperidol combination are shown in Table 1. In group A (bolus) dogs, changes in heart rate were not significant. In group B dogs (infused), the heart rate decreased after administration of the combination ketamine (8 mg/kg) / droperidol (1 mg/kg), but was not significantly different from baseline after 30 minutes of infusion. anesthesia. The maximum decrease in mean heart rate from baseline was greater in group B dogs, averaging 22 ± 9 beats / minute compared to group A dogs, averaging 7 ± 8 beats / minute.

Systolic, diastolic, and mean blood pressure values decreased significantly immediately after administration of the ketamine-droperidol combination to both groups and were not significantly different from baseline after 30 minutes of anesthesia. The maximum decrease in mean blood pressure compared to baseline values was much higher (38 ± 15 mmHg) in group A

dogs, compared to the value in group B dogs, respectively 18 ± 8 mmHg (Table 2.).

The effects of the ketamine-droperidol combination on pH and blood gas variables are shown in Table 3. Changes in PaCO2, PaO2 and changes in bicarbonate (HCO3-) concentration were not significant. pH and basic excess (EB) values fell below baseline at all-time intervals at which samples were taken and in both groups of dogs, but these changes were significant only in dogs in group B.

In the 6 dogs (3 in group A and 3 in group B), in which the experiment was repeated (after an interval of 14 days) only with acepromazine 0.5 mg/kg, intramusculary. The body temperature decreased significantly over time (during the monitoring period, 60 minutes). Significant increases in heart rate were observed over time and especially at 45 and 60 minutes (times when blood samples were taken) from baseline. Systolic, diastolic and mean blood pressure did not vary significantly over time. Changes in pH, PaCO2, PaO2, HCO3- and EB values were significant. Significant differences were recorded between the control group (n = 6) and group B or group A of dogs at each time interval.

DISCUSSIONS

When ketamine is given intravenously without preanesthesia in healthy dogs, heart rate and blood pressure increase (Haskins, S.C. et al., 1983; Vlerick L. et al., 2020). This response to ketamine is probably an indirect effect. Cardiostimulatory effects can be caused by various physiological mechanisms, including sympathomimetic effects mediated in CNS structures, intraneuronal and extraneuronal inhibition of catecholamine reuptake, and component vagal inhibition of the baroreceptor reflex (Mandsager R., 2003). With the exception of increases in heart rate, diazepam effectively "blocks" the cardiostimulatory properties of ketamine (Haskins, S.C. et al., 1986; Gebremedhin Y., 2018; Gebremedhin Y et al., 2018).

Cardiostimulatory effects may also be evident when higher doses of ketamine are used, and in dogs recovering from general anesthesia with isoflurane or when low doses of it are administered just before isoflurane anesthesia, or when ketamine is administered to humans during halothane or isoflurane anesthesia (Yasuda N. et al., 1991). In contrast, in combination with other anesthetics its action on cardiac properties is different. For example, in the combination of ketamine (28.4 mg / kg, i.v.) / haloperidol (1.42 mg / kg, i.v.), in addition to good muscle relaxation and analgesia, mean blood pressure (MAP) and volume tidal increase significantly (Kumar A., et al., 2001). In the combination of medetomidine (10 μg / kg) / propofol (4 mg / kg) / ketamine (10 mg / gc), administered intravenously, there was depression of cardiac activity (between 6 and 60 minutes), respiratory activity and a decrease in body temperature (Gulanber E., et al., 2001; Ozaydin J., et al., 2001).

In our study, acepromazine (0.5 mg / kg) effectively reduced the cardiorespiratory properties of the ketamine - droperidol combination. Rapid decreases in mean blood pressure in group A (bolus) dogs were probably attributed to decreased cardiac output. In group B (infusion), it appears that a marked decrease in heart rate also contributed to decreases in mean blood pressure, although in several studies ketamine induced positive inotropic effects (Miranda-Cortés A.E., et al., 2020). The results of most studies show that ketamine may have a negative inotropic effect on the myocardium (Hanouz JL., et al., 2004). We cannot say why significant decreases in heart rate are due to infusion of the ketamine / droperidol combination, but not after bolus administration. Probably, large decreases in mean blood pressure at group A (bolus) and any increase associated with sympathetic tone may have served to maintain heart rate.

Maximum decreases in mean blood pressure were much higher in group A than in group B and this indicates that depressant effects may be dose related. Blood pressure was lower in dogs in both groups (A and B) at minute 1 compared to dogs in the control group. This highlights the cardiovascular effects of the ketamine (8 mg/kg) -droperidol (1 mg / kg) combination.

The infusion technique has the advantage of administration control; In any case, it is observed that in group B, the decreases in mean blood pressure were the largest during the first 5 minutes of infusion. This would correspond to the peak concentration of ketamine in the plasma. Although the infusion dosage was lower, cardiovascular depression may be substantial.

From the 10th minute after administration of the ketamine / droperidol combination and until the end of the study, the changes in most variables were parallel to the changes in the control group dogs. Moreover, the rapid redistribution of ketamine may have influenced the immediate return of cardiovascular variables to baseline values. Although only decreases in arterial pH and

basal excess were significant in group B, in general, the decreases were close for dogs in both groups. Although the decreases were clinically insignificant, they indicate a mild metabolic acidosis, which may be the result of inadequate irrigation or oxygenation of the tissues.

The lack of a pressor response can be explained by changes in the activity of the autonomic nervous system during anesthesia. Autonomic activity is attenuated during acepromazine preanesthesia and, as a result, the cardiostimulatory properties of ketamine are not evident when the sympathetic response is blocked. Also, the sympathetic-tonic response to ketamine cannot be observed in critically ill patients due to catecholamine depletion and adrenocortical deposits (Erstad BL., et al., 2016).

There was an increase in mean blood pressure after ketamine administration, probably because the sympathetic (catecholamine) reserves were not depleted.

CONCLUSIONS

The results of the study show that the combination of ketamine (8 mg / kg) / droperidol (1 mg / kg) should be used with caution in dogs pre-anesthetized with acepromazine (0.5 mg / kg).

Infusion is preferable to bolus and induces an anesthetic effect for at least 30 minutes, long enough to perform diagnostic procedures and small-scale surgical procedures (sutures of skin wounds). The recovery of dogs from ketamine-droperidol infusion anesthesia was easy and fast without being accompanied by muscle stiffness, convulsions, vocalization, hypersalivation, etc., phenomena commonly encountered under ketamine anesthesia.

The advantage of preanesthesia with acepromazine (0.5 mg / kg, 15 minutes before the combination) would be to attenuate the activity of the vegetative system, "masking" to some extent the cardiostimulatory effects of ketamine in dogs.

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Table 1.

Mean values (± SD) of cardiovascular indices, bolus versus infusion

Variables	Administration	Basic values	Time								
			-10	-5	1	5	10	20	30	45	60
FC (beats / min.)	Bolus	111±8	ND	ND	107±9	109±7	108±8	108±6	109±6	111±6	109±9
	Perfusion	120±17*	97±14	99±8	103±11	104±16	103±15	104±16	106±13	112±14	117±12
SBP (mmHg)	Bolus	101±11*	ND	ND	55±10*	66±12	76±16*	81±14*	92±8*	97±8*	97±8*
	Perfusion	94±6*	80±4	74±4	73±4	78±4	85±3*	87±8	92±4*	93±8*	96±6*
DBP (mmHg)	Bolus	63±9*	ND	ND	33±4	37±8	49±14	43±4	56±9	58±8	58±9
	Perfusion	57±9*	44±3	40±4	41±3	47±7	54±4	51±8	53±8	53±6	56±9
ABP (mmHg)	Bolus	77±11*	ND	ND	40±7	46±10	58±15	56±5	68±9*	74±10	69±8*
	Perfusion	69±7*	55±6	51±7	53±3	58±3	63±5	63±6	66±8	69±7	72±7
T (0C)	Bolus	39.0±0.1*	ND	ND	38.7±0.7	38.6±0.7	38.4±0.6	38.6±0.6	38.6±0.6	38.7±0.7	38.5±0.8
	Perfusion	39.3±0.8*	38.7±0.1	38.3±3	37.8±0.3	37.7±0.5	37.8±0.5	37.9±0.2	37.5±0.5	37.4±0.4	37.7±0.6

Data are presented as M ± DS. Mean values with * are significantly different. FC- heart rate, SBP - systolic blood pressure, DBP - diastolic blood pressure, ABP - average blood pressure, T (0C) -temperature

Table 2.

Mean (± SD) values of maximal decreases in heart rate and mean blood pressure, bolus versus infusion

Variables	Group A (Bolus I.V.)	Group B (perfusion I.V.)
FC (beats / min.)	6 ± 7	23 ± 11
MAP (mmHg)	38 ± 15	18 ± 8

Data are reported as M ± DS. Significant differences $p < 0,05$. HR – heart rate; MAP – mean arterial pressure

Table 3.

Mean values (± SD) of the acid-base balance variables,
bolus (group A) versus infusion (group B)

Variables	Administration	Basic value	Time (minutes)		
			15	30	45
pH_a (U)	Bolus	7,364±0,065	7,322±0,045	7,304±0,027	7,292±0,033
	Perfusion	7,355±0,061*	7,316±0,043*	7,293±0,030*	7,306±0,049*
P_aCO_2 (mmHg)	Bolus	38,9±6,2	41,8±3,9	41,1±4,5	42,7±4,7
	Perfusion	39,4±4,4	41,8±3,7	41,3±3,8	42,3±3,1
P_aO_2 (mmHg)	Bolus	467,3±48,8	471,5±27,8	474,4±20,0	483,3±20,9
	Perfusion	473,9±42,0	496,9±39,7	490,5±62,7	492,9±40,9
HCO_3^- (meq/l)	Bolus	20,3±1,5	20,5±2,0	21,0±2,7	21,6±1,0
	Perfusion	21,9±1,3	21,3±1,0	20,1±2,6	21,1±1, 1
BE (meq/l)	Bolus	-3,9±1,6	-4,9±1,7	-5,4±1,7	-4,9±0,5
	Perfusion	-2,9±2,5*	-4,5±1,6*	-6,0±2,7*	-4,8±2,1*

Data are presented as M ± DS. Mean values with * significantly different ($p < 0.05$).
pHa - blood pH, PaCO2 - blood pressure CO2, PaO2 - blood pressure O2,
HCO3- bicarbonate concentration, BE - basic excess