Continuous infusion in adult females dogs submitted to ovariohysterectomy with midazolam-xylazine and/or medetomidine pre-treated with methotrimeprazine and buprenorphine[1]

Infusão continua em cães fêmeas submetidas à ovariohisterectomia com midazolam/cetamina/xilazina e/ou medetomidina pré-tratadas com levomepromazina e buprenorfina

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ABSTRACT

Purpose: To compare, by continuous infusion of ketamine or medetomidine combined to methotrimeprazine and buprenorphine, ketamine and midazolam, the degree of hypnosis, myorelaxation, anesthetic quality and surgical feasibility through evaluation of possible parametric alterations and recovery quality. **Methods**: 20 healthy adult females dogs, aged 3 to 5 years, body weight between 7 and 15 kg, were assigned randomly and homogenously to 2 groups of 10 animals each (n=10), group 1 (G1) and group 2 (G2), respectively. Animals of G1 were subjected to a pre-treatment with intravenous 1.0 mg/kg methotrimeprazine and or 3ì/kg. After 15 minutes, a 5.0 mg/kg ketamine and 0.2 mg/kg midazolam were intravenously injected. Immediately after induction, an anesthetic combination of 0.4 mg/kg/h midazolam, 20 mg/kg/h ketamine and 1.0 mg/kg/h xylazine, was continuously and intravenously administered for 30 minutes. The same techniques were used in G2 except for the substitution of xylazine for 30ìg/kg/h medetomidine. **Results**: In G1 there was a 1st and 2nd degree atrioventricular heart block, a longer recovery period and lower quality. In G2 a 1st degree atrioventricular heart block occurred but isolated and ephemeral. **Conclusions**: The continuous infusion method, besides reducing drugs utilization, prevented collateral effects allowing a more tranquil recovery with no excitations, both protocols permitted the surgical procedure (ovary-hysterectomy) bringing about a reduction in hypnosis and an accentuated myorelaxation. Xylazine and medetomidine showed a similar pharmacodynamic behavior but with different clinical aspects. The electrocardiographic alterations observed in G2 and in a lower degree in G1 must be well studied. Describers: dogs, ketamine, methotrimeprazine, medetomidine, midazolam and xylazine.
Key words: Methotrimeprazine. Medetomidine. Midazolam. Xylazine. Dogs.

RESUMO

Objetivo: Comparar através de infusão contínua de xilazina ou medetomidina associada à metotrimeprazina e buprenorfina, cetamina e midazolam, o grau de hipnose, miorrelaxamento e qualidade anestésica e a viabilidade cirúrgica, avaliando eventuais alterações paramétricas e qualidade de recuperação. **Métodos**: Foram utilizados 20 cães fêmeas, adultas, hígidas (3 a 5 anos de idade) com peso corporal entre 7 e 15 quilos, escolhidas e distribuídas aleatoriamente de forma homogênea em 2 grupos de 10 animais cada, (n=10) sendo estes designados por Grupo 1 (G1), e Grupo 2 (G 2). Em G1, os animais foram submetidos a um pré-tratamento com metotrimeprazina na dose de 1,0 mg/kg e buprenorfina na dose de 0,003mg/kg ou 3 µg/kg intravenoso. Decorridos 15 minutos, administrou-se cetamina na dose de 5,0 mg/kg e midazolam na dose de 0,2 mg/kg intravenoso. Imediatamente após a indução iniciou-se administração contínua, por um período de 30 minutos, da associação anestésica de midazolam 0,4 mg/kg/h, cetamina 20mg/kg/h e xilazina 1,0 mg/kg/h IV. Em G 2 utilizou-se a mesma técnica empregada em G1 substituindo-se, a xilazina pela medetomidina na dose de 30µg/kg/h. **Resultados**: Verificou-se em G1 bloqueio átrio-ventricular de primeiro e segundo grau, período de recuperação mais longo além de menor qualidade. Em G 2 observou-se bloqueio átrio-ventricular de primeiro grau isolado e de ação fugaz. **Conclusões**: Ao se aplicar o método de infusão contínua, além da redução dos fármacos aplicados, evitaram-se efeitos colaterais permitindo uma recuperação mais tranqüila e isenta de excitações, ambos os protocolos permitiram a realização do ato cirúrgico (ovário-salpingo-histerectomia), causando uma redução da hipnose e um miorrelaxamento acentuado. A xilazina e a medetomidina apresentam um comportamento farmacodinâmico semelhante, porém com aspectos clínicos diferentes, as alterações eletrocardiográficas observadas em G 2 e em menor grau em G1 devem ser melhor estudadas.
Descritores: Metotrimeprazina. Medetomidina. Midazolam. Xilazina. Cães.

Introduction

Many dissociative anesthetic combinations have been efficiently used in the veterinary surgical routine. However, sometimes these combinations were unable to provide a suitable degree of hypnosis and analgesia needed for the surgical procedures. During anesthesia, monitorization is important for, besides allowing a better clinical evaluation permits, also, to forecast some possible disturbs that adversely affects the anesthetic procedure quality and even situations that bring about a serious discomfort status to the patient. The continuous evaluation of the patient, added to a good anesthetic procedure quality is fundamental, allowing carrying out more quality anesthesias, providing more safety and comfort to the patient during the surgical procedure. The coadministration of biotransformed substances in the liver can extend the dissociative drugs half-life due to the competition with hepatic enzymes and there are many anesthetic groups which inhibit the adverse effects of these pharmakos. Data obtained from electroencephalograms, by 1980, were utilized to create a parameter known as the Bispectral Index Scale (BIS) which consists of a numerical value derived from the electroencephalogram obtained through the BIS monitor which quantifies the consciousness and awareness status. It is also applied in the anesthesiology routine for being a measure of the hypnotic and sedative effects of the anesthetic drugs. The monitoring of the BIS has been largely used in humans but in a lower number in veterinary medicine works.

Methods

This research was approved by the Ethics Committee of Animal Experimentation. Twenty healthy mongrels adult female dogs, submitted to clinical and biochemical routine tests, aged 3 to 5 years and body weight between 7 and 15 kg were used. To decrease data fluctuations related to individual physiological variations, animals were homogenously and randomly distributed, as for age and clinical condition, in two groups of 10 animals each (n=10), numerically individualized in a crescent order, being group 1 (G1) and group 2 (G2), respectively. In G1, animals were subjected to a pre-treatment with intravenous injection of 1.0 mg/kg methotrimeprazine and 3ìg/kg buprenorphine. After 15 minutes, 5.0mg/kg ketamine and 0.2 mg/kg midazolam were intravenously administered. Immediately after induction, a 0.4 mg/kg/h midazolam, 20 mg/kg/h ketamine and 1.0 mg/kg/h xylazine combination was intravenously and continuously administered for 30 minutes. The same techniques were used in G2 except for the change of xylazine for medetomidine at 30ug/kg/h. In both groups, the continuous infusion period lasted for 30 minutes. After

being in the syringe, the maintenance drugs were completed up to 20 ml with bidistilled water solution. The parameters were taken and evaluated at the following moments: M0, immediately before pre-treatment; M1, 15 minutes after pre-treatment and immediately before anesthetic induction; M2 - M4, measurement at each 10 minutes immediately after anesthetic induction and the beginning of continuous infusion. All animals were submitted with a previous fluidtherapy (20 ml/kg/h) to ovariohisterectomy and when induced, intubated and maintained in spontaneous respiration during surgery, measuring during proposed moments the parameters: rectal and/or esophageal temperature, respiratory frequency (*f*), tidal volume(V_T), minute volume(V_M) SpO_2, $EtCO_2$, $EiCO_2$, FiO_2, $FiCO_2$, cardiac frequency(CF), systolic arterial pressure (SAP), medial arterial pressure (MAP), diastolic arterial pressure (DAP), Bispectral Index Scale (BIS) and electromyography (EMG). The profile analysis was applied to data through the Software SPSS 12.0 Windows, Advanced Statistical Package for Social Science (ASPSS) for $P < 0.05$.

Results

In both groups there was a decrease in rectal (RT) and/or esophageal (OT) temperature but attaining less than 1.0^oC with no statistical or clinical relevance. Respiratory frequency (*f*) gradatively decrease in both groups but attained the normal or basal levels from M3 onward, in G2 only. The tidal volume (V_T) decreased in both groups, but increased during anesthetic maintenance although at different moments in each group. In G2, the O_2 saturation ($SatO_2$) remained stable within the physiological parameters at all moments but an increase occurred in G1 from M2 to M4. The CO_2 tension ($EtCO_2$) at the end of expiration, in G1, showed an increase from M2 to M4 in G1 . In both groups, an accentuated increase in O_2 tension at the end of expiration (EtO2) took place from M2 onward. The CO_2 inspired fraction ($FiCO_2$) constantly increased at all moments, in both groups, with the highest value at M3 and an accentuated increase in the O_2 inspired fraction from M2 onward with O_2 administration. A slight decrease in the cardiac frequency (CF) took place from M0 onward but still within the physiological parameters. In spite of this reduction, there was no bradycardia occurrence. However, electrocardiographic alterations were observed in D-II derivation in animals of G1 and G2. In G1, three animals showed atrioventricular heart block, (AVB), two showed a 1st degree AVB at M2 with no replication thereafter and a 2nd degree AVB at M3. Only one animal showed a 1st and 2nd degree in G2, isolated and with no replication. The average systolic (SAP) and diastolic (DAP) arterial pressure were reduced in both groups, but hypotension was not characterized, with minimum oscillations

occurrence along the moments. In both groups, a reduction in the BIS was observed at all moments, particularly from M2 to M4 with the lowest value at M4, in G2. The electromyography (EMG) decreased continuously and permanently at all moments in both groups. (Table 1) In both groups during the surgical procedure, no significant reactions were observed as well a when the ovarioyhysterctomy was made. The recovery was more calm in G2 than G1 (five animals) when vocalizations, shivering and difficulties for the postural tonus recovery. No reactions were observed during surgery when the ovary pedicle was nipped in both groups. A shorter anesthetic recovery period occurred in G2 (48 min) as compared to G1 (52 min) and, also with a superior quality.

TABLE 1 - Anesthetic evaluation (means and standard -deviations) in adults females dogs treated with midazolam-xylazine-ketamine (G1) or midazolam-medetomidineketamine (G2)

Variable	Groups	M0	M1	M2	M3	M4
T (ºC)	G1	38,11±0,42	37,9±0,53	37,35±0,98	37,22±0,99	37,12±0,91
	G2	37,43±0,50	37,21±0,72	36,74±0,88	36,64±0,76	36,41±0,76
f (mov/min)	G1	30,9±13,84	18,7±9,37	11,9±4,70	18,5±13,16	13,4±6,06
	G2	26,6±8,93	17,1±7,36	17,5±10,43	21,5±12,30	20,4±9,05
V_T (ml/kg)	G1	247,6±123,97	228,1±115	246,8±100,59	162,3±78,23	201,7±97,62
	G2	245,2±167,96	209,8±77,75	166,6±93,35	180,8±88,44	163,7±146,55
V_M (L/min)	G1	7,01±3,10	3,68±1,57	3±2,10	2,4±1,25	2,33±1,22
	G2	5,67±2,04	2,97±0,84	2,94±2,29	3,43±1,59	2,03±0,80
$SptO_2$ (%)	G1	96,5±0,97	96±2,21	98,2±1,62	97,3±2,21	97,6±2,41
	G2	97,6±1,17	97,7±0,82	96,6±1,90	97,2±2,20	97,2±2,78
E_tCO_2 (mm/Hg)	G1	22,6±4,97	28,8±8,02	43,4±6,95	45,6±5,76	47±5,94
	G2	30,3±4,95	30,9±3,70	37,4±7,44	42,3±7,35	42±3,33
E_tO_2 (mm/Hg)	G1	15,9±1,91	16,1±2,47	79,6±10,22	84,2±5,88	85,3±3,74
	G2	15,2±3,29	18,5±6,13	82,5±10,36	83±10,83	84,2±10,81
F_iCO_2 (%)	G1	1,7±0,95	2,1±0,74	2,4±1,96	3,7±2,50	3,2±1,75
	G2	1,8±0,92	2,3±0,82	3,1±1,10	4,2±1,62	3,6±1,07
F_iO_2 (%)	G1	20,4±0,52	20,5±0,71	87,8±9,19	91±4,35	92,4±2,37
	G2	20,8±0,63	22±2,31	80,8±21,09	81,6±22,09	90,5±5,36
CF	G1	119,8±19,88	103,5±19,06	100,2±8,42	97,1±17,94	95,2±19,46
	G2	121,3±22,63	107,4±26,59	99,1±25,44	99,8±27,34	99,5±25,05
SAP (mm/Hg)	G1	134,8±13,83	129,7±12,79	127,9±20,28	127,8±16,67	121,3±17,75
	G2	125,6±20,30	114,5±14,51	119,3±12,25	123,8±18,63	120,1±16,84
MAP (mm/Hg)	G1	101,9±14,29	97,2±13,85	103,9±23,43	103,5±14,10	97,1±16,45
	G2	105,6±18,05	93±11,57	100,7±15,39	104,5±16,04	99,9±14,95
PAD (mm/Hg)	G1	88,1±15,31	82,8±14,62	89,7±27,32	94,5±12,89	89,1±15,98
	G2	91,6±17,60	74,8±11,16	91,3±16,36	94,3±19,47	89,5±15,70
BIS	G1	98,5±0,71	98,3±0,48	80,9±6,94	71,9±7,94	68,1±7,03
	G2	98,8±0,42	98,3±0,48	81,7±4,50	72,5±5,40	65,,2±8,20
EMG (%)	G1	100,0±0	85±6,48	43,1±9,97	31±8,68	25±6,94
	G2	99,9±0,32	86,4±3,53	44,3±14,48	31,5±8,89	25,1±6,49

Discussion

Rectal (RT) and/or esophageal (TO) temperature decreased slightly and gradatively by less than 0,99°C what has also been reported for different dissociative anesthesia protocols through continuous infusion [2,3,4]. A greater reduction in body temperature as observed by some authors [5,6,7] is due to the peripheral vasoconstriction and blood central redistribution due to the action of a-2 agonists. This is a controversial effect for a-2 agonists lead to peripheral vasodilatation and heat production reduction. Different dissociative anesthesia protocols used by some authors [10,11] showed a greater decrease in RT as related to methotrimeprazine effects when used in the combination, as cited before [12]. Both groups showed a decrease in respiratory frequency (*f*) but still within the physiological limits (10-40 breaths/min)[9], also observed in dogs treated with atropine/romifidine/ketamine [13]. No relevant alterations

occurred [14, 15, and 16] in f when the treatment was with a combination of medetomidine to other drugs dogs treated with medetomidine/butopharnol/midazolam showed bradypnea which could be associated to the butopharnol administration[19] and in dogs treated with medetomidine/butopharnol/ketamine. This was not observed in G1 and G2. This combination can cause a transient apnea during the anesthetic induction in pre-treated dogs with medetomidine/midazolam[20]; however the other respiratory parameters showed no relevant reduction, including up to 62% in dogs treated with a intramuscular injection of medetomidine/buprenorphine [21]. In G2 there was a slight decrease in V_T which remained stable after the beginning of the anesthetic maintenance. This stability also occurred in G1 but with oscillations along the moments as reported earlier[22] in dogs subjected to medetomidine/butopharnol/midazolam [14]. In both groups there was a decrease in V_M as reported before[11], in dogs subjected to methotrimeprazine/ketamine/xylazine and in dogs treated with medetomidine/ and medetomidine/butopharnol[14]. This reduction was more relevant in G1 although with greater values as compared to G2. This behavior can be based on the depressing effect of xylazine on f [23,24]. The relationship between V_T and f showed that the greatest alteration was related to xylazine confirming, once again, the compensatory phenomenon. It is known that there is an inverse proportion, i.e., decrease in f -increase in V_T. This was slighter in G2. The pre-oxygenation of dogs treated with medetomidine/diazepam/ketamine is always recommended [6] to avoid hypoxemia, what was confirmed by the results of this experiment from M2 on. When checking whether or not there was an appropriate ventilation through $EtCO_2$[26], normal values were found [27] (35 and 45 mmHg) and so, 1 to 3 mmHg below PaCO2. In G1, however, a value greater than normal was observed at M4 what is probably associated to the reduction in V_M and SatO2, as a result of the alterations brought about by xylazine [11], confirmed when intramuscular ketamine and xylazine injection was used. In both groups the cardiac frequency (CF) behavior was similar showing a slight decrease, but within the physiological limits, as reported for pre-treated dogs with intravenous buprenorphine [28] leading to. This reduction can be associated to the depressing effects of methotrimeprazine [29] by a CF decrease in pre-treated dogs with methotrimeprazine and treated with a-2 agonists, probably due to the increasing tachycardia effect caused by ketamine through the direct synaptic stimulation by elevation of circulating norepinephrine. The increase in the membrane cells permeability excites the conductors by the action of norepinephrine[30, 31, 32] favoring the passage of Na+, making the fibers more excitable and, as a result, avoiding or increasing bradycardia. Although bradycardia has been observed in pre-treated dogs with medetomidine and treated with propophol, [34] that has not occurred in pre-treated dogs with medetomidine or dexmedetomidine and treated with propofol/isoflurane, probably due to the continuous

infusion with medetomidine/fentanyl or fentanyl using the above cited technic.[15, 35] Also, no bradycardia occurred in dogs treated with medetomidine/midazolam/butopharnol. When in "bolus" was intravenously administered, opposite results were found as compared to those obtained by some authors[36, 37] whom found a dose-dependent cardiovascular depression in dogs treated with different dosis of intravenous medetomidine. It was observed a more accentuated CF decrease in dogs treated with medetomidine as compared to those treated with xylazine. An alteration in the ECG was caused by dissociative drugs, but no disturbs were generated in the rhythm. However, both groups showed a cardiac arrhythmia with 1st and 2nd degree atrioventricular block (AVB) in an isolated and ephemeral case in G2, with a higher incidence in G1. This can be related to a higher sensitivity to a-2 and a-1 receptors, in medetomidine when compared to xylazine or other a agonists[3, 38, 39]. These effects can be explained by the xylazine action leading to a 1st, 2nd and even 3rd degree AVB , even when low dosis are used. The phenotiazínics have been recommended as antiarrhythmogenic producers [18 41, 42], however, in this work, an atrioventricular block (AVB) occurred when the intravenous continuous infusion was undertaken but at a lower level by the change of xylazine for medetomidine. Soon after anesthetic premedication, a slight reduction in systolic arterial pressure (SAP), medial arterial pressure (MAP) and diastolic arterial pressure (DAP) was obtained in both groups, assumed as buprenorphine effects following the intravenous or intramuscular injection in dogs [43,44] besides a slight hypotension [24]. Nevertheless, all the values remained within the physiological limits, 100 to 160 mmHg, 80 to 120 mmHg and 60 to 100 mmHg, respectively, in both groups, at all moments. These values can be due to the ketamine action that leads to a peripheral vasoconstriction, as earlier reported [45], by efficiently antagonizing the depressing effects brought about by methotrimeprazine, combined, moreover, to a 20 ml/kg/h fluidtherapy undertaken during the intravenous continuous maintenance. As for the Bispectral Index Scale (BIS), a slight reduction occurred when animals were already under pre-treatment [46]. After the beginning of intravenous continuous infusion using the proposed combinations, BIS showed a more relevant reduction, in opposition to results found by other authors[47, 48, 49] to whom BIS is not appropriate to apply in patients treated with ketamine. Such phenomenon can be explained by the increase in hypnosis degree caused by the benzodiazepine/a-2 agonist/opioids combination. In man, when only 0.01 mg/kg midazolam is utilized, a decrease in BIS occurs while an immediate increase in this parameter is found, but this effect is suppressed by the sedative and/or hypnotic and synergic a-2 agonist action, and the benzodiazepínic combined to the dissociative drugs for the anesthetic maintenance. The first report on the interaction between a-2 agonists and benzodiazepínics related the postural tonus and the labyrinth test in rats, [52] concluding

for the existence of a synergism process in this interaction, which was classified as an intense one, through a pharmacodynamic study in rats [53]. However, the precise cause of this synergic action is still unknown [54]. This reduction in BIS is supported by data obtained from utilization of medetomidine in electroencephalography, [55] either in low or high frequency. In dogs treated with medetomidine/isoflurane or isoflurane only , there was an accentuated decrease in BIS as compared to dogs treated with isoflurane only, and so, in conformity with the same authors [56, 57, 59]. In both groups the electromyography was more accentuated from M2 to M4 characterizing the synergism among the a-2 agonist, buprenorphine and midazolam which suppressed the cataleptoid effects of ketamine and the presence of muscular tonus due to ketamine, the same observed by an author [4], but not observed by others [11, 46, 60] The reported recovery period is variable [10], around 76 or down to 64 minutes, approximately. The values were lower than those obtained by other authors and showed that the continuous infusion has an advantage for no significant alterations occurred in the physiological parameter, a better quality and decrease the drugs mass dosis to be utilized.

Conclusions

It was concluded that both a-2 agonists (xylazine and medetomidine) cause a reduction in hypnosis degree producing an accentuated myorelaxation with a similar parametric behavior but with different clinical aspects. and the anesthetic recovery was shorter and showed a better quality in G2 as compared to G1. In the proposed anesthetic combination, either xylazine or medetomidine allowed tranquility during the surgical procedure without any apparent discomfort except for the presence of electrocardiographics alterations, more relevant in G1.Yet, when the continuous infusion method was applied, besides the reduction in the amount of drugs used, collateral effects were avoided, allowing a more tranquil recovery, with no excitations observed.

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