

Effect of acepromazine as an adjuvant to ketamine, midazolam and methadone in the chemical restraint of cats

Efeitos da acepromazina como adjuvante a cetamina midazolam e metadona, na contenção química de gatas

Efectos de la acepromazina como complemento del midazolam de ketamina y la metadona sobre la contención química de gatos

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Abstract

This study aimed to evaluate the effectiveness of acepromazine as an adjuvant to ketamine, midazolam and methadone in the chemical restraint and anesthesia of cats undergoing ovariohysterectomy. We allocated 14 cats in two groups: group ketamine (GK), premedicated with ketamine 8 mg/kg, midazolam 0.3 mg/kg and methadone 0.3 mg/kg and group acepromazine (GAK), premedicated with acepromazine 0.05 mg/kg in addition to the above-mentioned drugs. At baseline (T0) and every 5 mins up to 20 mins (T5, T10, T15 and T20) after premedication, the sedation score was evaluated at 0 to 24 points. The sedation score was significantly higher at T5, T10, T15 and T20 in both groups. There were no significant differences in extubation times (3.7 ± 1.3 mins in GK; 5.2 ± 2.6 mins in GAK) and the time to reach

a score equal to 0 on the sedation scale (88 ± 63.9 mins in GK; 133 ± 39.7 mins in GAK); however, the time of anesthetic release was significantly higher in the GAK than in GK (19.7 ± 6.5 mins vs 11 ± 5.9 mins) ($P = 0.023$). Sedation was adequate in both groups. The results indicated that the administration of acepromazine did not contribute to sedation in the protocol and could delay the anesthetic release.

Keywords: Anesthesia; Sedatives; Preanesthetic Medication; Dissociative Anesthesia.

Resumo

O objetivo desse estudo foi avaliar o efeito da acepromazina com adjuvante ao protocolo de cetamina, midazolam e metadona na contenção química e anestesia de gatos submetidas a ovariosalpingohisterectomia. Os animais foram divididos em dois grupos: grupo cetamina (GK), premedicados com cetamina 8 mg/kg, midazolam 0,3 mg/kg e metadona 0,3 mg/kg, e o grupo acepromazina (GAK), premedicados com acepromazina 0,05 mg/kg associada aos fármacos citados anteriormente. No momento basal (T0) e a cada 5 minutos até 20 minutos (T5, T10, T15 e T20), após a premedicação, um escore de sedação foi avaliado de 0 a 24 pontos. A sedação foi significativamente maior nos T5, T10, T15 e T20 em ambos os grupos. Não teve diferença significativa nos tempos de extubação (3.7 ± 1.3 minutos no GK; 5.2 ± 2.6 minutos no GAK); e no tempo para alcançar escore igual a 0 na escala de sedação (88 ± 63.9 minutos no GK; 133 ± 39.7 minutos no GAK); entretanto, o tempo de alta anestésica foi significativamente maior no GAK do que no GK (19.7 ± 6.5 minutos contra 11 ± 5.9 minutos) ($P = 0.023$). A sedação foi adequada em ambos os grupos. A administração de acepromazina não contribuiu para a sedação e aumentou o tempo de alta anestésica.

Palavras-chave: Anestesia; Sedativos; Medicação Pré-anestésica; Anestesia dissociativa.

Resumen

El objetivo de este estudio fue evaluar el efecto de la acepromazina con adyuvante al protocolo de ketamina, midazolam y metadona sobre la contención química y la anestesia de gatos sometidos a ovariosalpingohisterectomía. Los animales fueron divididos en dos grupos: grupo ketamina (GK), premedicado con ketamina 8 mg/kg, midazolam 0,3 mg/kg y metadona 0,3 mg/kg, y el grupo acepromazina (GAK), premedicado con acepromazina 0,05 mg/kg asociado a los fármacos mencionados anteriormente. Al inicio (T0) y cada 5 minutos hasta 20 minutos (T5, T10, T15 y T20), después de la premedicación, se evaluó un puntaje de sedación de 0 a 24 puntos. La sedación fue significativamente mayor en T5, T10, T15 y T20 en ambos grupos. No hubo diferencias significativas en los tiempos de extubación ($3,7 \pm 1,3$ minutos en GK; $5,2 \pm 2,6$ minutos en GAK); y a tiempo para lograr una puntuación igual a 0 en la escala de sedación ($88 \pm 63,9$ minutos en GK; $133 \pm 39,7$ minutos en GAK); sin embargo, el tiempo de descarga anestésico era perceptiblemente más largo en GAK que en GK ($19,7 \pm 6,5$ minutos contra $11 \pm 5,9$ minutos) ($P = 0,023$). La sedación fue adecuada en ambos grupos. La administración de acepromazina no contribuyó a la sedación y aumentó el tiempo de anestésico alto.

Palabras clave: Anestesia; Sedantes; Medicación Préanestésica; Anestesia Dissociativa.

1. Introduction

When a cat has been administered a preanesthetic medication the aim is to reduce the stress of the cat and facilitate manipulation by the veterinarian, thus promoting chemical restraint (Volpato et al., 2014). The use of drug combinations can improve sedation, with lower doses and fewer side effects (Mocholi, Belda, Bosmans & Laredo 2016).

In the veterinary anesthetic routine, one of the most commonly used protocols for the sedation of cats when a preanesthetic is used, is the combination of ketamine, midazolam and an opioid. This combination aims to promote dissociative anesthesia, muscle relaxation, transoperative analgesia and postoperative analgesia (Fantoni & Garofalo, 2012; Moreno, 2012; Rankin, 2015).

Ketamine has a depressing effect on the myocardium and it ends up stimulating the sympathetic nervous system (Ingwersen, Allen, Dyson, Pascoe, O'Grady, 1988). This action increases the heart rate, cardiac output and blood pressure (Pawson & Forsyth, 2010). These effects can be reduced with the use of an adjuvants drug, like acepromazine, because this drug is a tranquilizer that produces depression in the central nervous system, vasodilatation and antiarrhythmic effects, and these effects have already been found in studies with dogs (Rankin, 2015; Monteiro, Rabello, Rangel, 2019).

We hypothesized that the addition of acepromazine to this protocol may improve the cardiovascular stability, sedation and anesthetic recovery in cats, in addition to producing dissociative anesthesia, muscle relaxation, sedation and analgesia. The

objective of this study is to evaluate the sedative effect of acepromazine in association with ketamine, midazolam and methadone in cats subjected to elective ovariohysterectomy (OH).

2. Methodology

Fourteen healthy cats subjected to elective OH were admitted to the Veterinary Hospital of the Federal University of Pelotas (HCV-UFPEL), between March and July 2018. The animals were of indefinite breed, ranged from 9 months to 5 years of age and underwent clinical and laboratory examinations before the anesthetic and surgical procedures. For the surgical procedure, the animals fasted for 12 h. The animals went through an acclimation period of at least 24 hours, in light and dark cycles of 12 hours each. On the day of surgery, they underwent a preanesthetic evaluation wherein their heart rate (HR), respiratory rate (RR), capillary filling times, temperature (T°C), hydration, mucous color, cardiac and pulmonary auscultation and blood counts were evaluated. The cats were classified according to the classification system of the American Society of Anesthesiologists (ASA), and only those categorized as ASA I, considered healthy animals, were selected for the study (Brodgelt, Flaherty, Pettifer, 2015). The cats were randomly allocated to two different groups (n=7) and the groups received the following preanesthetic medications: GK - ketamine 8 mg/kg (Dopalen, ketamine, Ceva, Brazil), midazolam 0.3 mg/kg (Dormire, midazolam, Cristália, Brazil) and methadone 0.3 mg/kg (Mytedom, metadona, Cristália, Brazil) and GAK (acepromazine 0.05 mg/kg (Acepran; acepromazina, Vetnil, Brazil), ketamine 8 mg/kg, midazolam 0.3 mg/kg and methadone 0.3 mg/kg). In both groups, the drugs were administered in the same syringe intramuscularly at a time T0. After the administration of preanesthetic, the cats were evaluated at 5, 10, 15 and 20 mins using a sedation scale that added the scores of six different independent parameters (Table 1).

Table 1. Modified numerical rating scale (scores from 0 to 4; 0 = low, 4 = high) of six independent parameters used to assess sedation and anesthesia. Sedation is considered to be poor (score 0–3), mild (4–6), moderate (7–10) and profound (11–15) based on the scores. If the score is >15, allowing intubation of the animal, it will be considered a state of anesthesia

Parameter	Response	Value
Spontaneous position	Able to stand and walk	0
	Sedated but standing or sitting	1
	Lying down but able to react quickly or stand up	2
	Lying down but reacting slowly and has difficulty in standing up	3
	Lying down and unable to stand up	4
Resistance to lateral recumbency	Strong resistance	0
	Moderate resistance	1
	Slight resistance	2
	No resistance	3

Response to noise	Normal response	0
	Listens and moves	1
	Listens and ear moves	2
	Hardly perceives	3
	No response	4
Jaw relaxation	Normal	0
	Slightly reduced	1
	Greatly reduced	2
Eyelid reflex	Normal	0
	Depressed reflex	1
	No reflex	2
Response to pain	Normal (withdrawal of the limb at a minimal clamping pressure)	0
	Slow response (withdrawal at a higher clamping pressure)	1
	Very slow response (withdrawal at a higher clamping pressure maintained for 3 to 5 s)	2
	No response	3

Source: Mocholi et al. (2016)

After the evaluation, venous catheterization was performed, and the animals were maintained on fluid therapy with lactated Ringer's solution administered at a rate of 5 mL/kg/h. As antibiotic prophylaxis, the animals received an intravenous dose of cephalothin (Cefalotina Sódica, cephalothin, Biochimico, Brazil) 25 mg/kg. For anesthetic induction, propofol (Propovan; propofol, Cristália, Brazil) was administered at a rate of 1 mg/kg/min until intubation was possible. The animals were then intubated and kept under general inhalation anesthesia with isoflurane (Isoforine; isoflurane, Cristália, Brazil) using calibrated vaporizers. The anesthetic circuit used was baraka. We evaluated the parameters of HR, RR, systolic blood pressure (SBP) by doppler method, T°C and oxygen saturation at seven moments: presurgical (M1), during skin incision (M2), opening of the abdominal cavity (M3), clamping of the right ovarian plexus (M4), clamping of the left ovarian plexus (M5), suturing of the abdomen (M6) and suturing of skin (M7). The surgical technique used followed the steps: retroumbilical incision of the skin and muscles, about 3 cm; exposure of the uterine horns; a window was made in the mesovary caudal to the ovarian artery and vein, followed by clamping using the three clamp technique (kelly clamp); section between first and second clamp; a circular suture was made with polyglactin 910 3.0 thread (Poliglactina 910, glycolid L 90%- lactide 10%, Shalom, Brazil) distal to the third clamp; the process was repeated in the other uterine horn; the cervix was located, and using the three clamps technique (kelly calmp), the uterus was removed, and thus a transfixing suture was made around the uterine stump; to suture

the musculature and subcutaneous tissue, a simple continuous pattern with polyglactin 910 3.0 thread (Poliglactina 910, glycolid L 90%- lactide 10%, Shalom, Brazil) was used; for suturing the skin, simple isolated stitches were made with nylon 3.0 (Nylon 3.0, black class II monofilament, Shalom, Brazil) thread. In the event of an increase in the parameters by 20%, fentanyl (Fentanest; fentanyl, Cristália, Brazil) 5 mcg/kg was administered intravenously. In the immediate postsurgical period, the animals received 0.1 mg/kg of meloxicam (Maxican; meloxicam, Ourofino, Brazil) and 25 mg/kg of dipyrone (D-500; dipyrone, Zoetis, Brazil), both intravenously. At the end of the surgery, extubation and recovery times were measured. To assess the recovery time, the Aldrete scale modified for anesthetic release score, was used, that is, the time it took the animals to reach a score greater than 8 was measured according to the scale. (Table. 2). We prescribed meloxicam 0.05 mg/kg every 24 h for 3 days, tramadol hydrochloride 2 mg/kg every 8 h for 5 days and dipyrone 25 mg/kg every 8 h for 5 days.

Table 2. Aldrete scale, modified for anesthetic release score, used at the Veterinary Hospital of the Faculty of Veterinary Medicine and Animal Science at the University of São Paulo

Parameter	Response	Value
Consciousness	Alert	2
	Responsive	1
	Nonresponsive	0
Respiratory system	RR>10 (breaths minutes)	2
	RR<10 (breaths minutes)	1
	Dyspnea/tachypnea	0
Airway	Absence of secretion	1
	Presence of secretion	0
Circulatory	Strong pulse	2
	Weak pulse	1
	Filiform pulse	0
Mucous colors	Roseas	2
	Pale	1
	Cyanotic	0

Source: Martins & Fantoni (2010)

All procedures involving the production, maintenance or use of animals for scientific research (or teaching) purposes are in accordance with the provisions of Law No. 11,794 of 8 October 2008, Decree No. 6899 of 15 July 2009 and the rules issued by the National Council for the Control of Animal Experimentation (CONCEA). Our study received a favorable opinion for its execution by the Ethics Committee on Animal Experimentation, registered with number 23110.001080 / 2018-14. Informed consent was obtained from the respective owners. For statistical evaluation of the degrees of sedation, we used the

Friedman test followed by Dunn's test between times and Mann–Whitney U test between groups; for other parameters, we performed an ANOVA followed by the Dunnett's test between times and Student's *t*-test between groups ($P \leq 0.05$).

3. Results

There were no observed statistical differences with regard to the values of age, weight and surgical time of the animals studied. The GK had an average age of 12.5 ± 4.7 months, whereas the GAK had an average age of 15.8 ± 9.5 months. When we assessed the weight data, GK had an average weight of 3.0 ± 0.5 kg and GAK, 2.9 ± 0.5 kg. In the surgical time evaluation, an average of 74.28 ± 31.94 mins was obtained in the GK, whereas in the GAK, this average was 70 ± 15.11 mins.

Using the sedation scale, statistically significant difference scores were observed at different times, starting from T0, in both groups. There was an increase in the degree of sedation with time, but there was no significant difference in the sedation between the groups (Table. 3).

Table 3. Sedation score values in cats premedicated with ketamine, midazolam and methadone (group ketamine [GK]) or with acepromazine, ketamine, midazolam and methadone (group acepromazine [GAK]), at baseline, T5 (5 mins after preanesthetic), T10 (10 mins after preanesthetic), T15 (15 mins after preanesthetic) and T20 (20 mins after preanesthetic).

Group	Measure	T0	T5	T10	T15	T20
GC	Minimum	0,0	1,0	8,0	8,0	6,0
	25° quartile	0,0	1,0	9,0	9,0	10,0
	Median	0,0	7,0	10,0 A	11,0 A	12,0 A
	75° quartile	0,0	8,0	11,0	12,0	14,0
	Maximum	0,0	10,0	15,0	16,0	15,0
GAC	Minimum	0,0	3,0	3,0	8,0	8,0
	25° quartile	0,0	4,0	8,0	10,0	10,0
	Median	0,0	8,0	12,0 A	13,0 A	13,0 A
	75° quartile	0,0	13,0	13,0	13,0	14,0
	Maximum	0,0	14,0	15,0	16,0	16,0

†A: different from T0 Mann–Whitney, $P \leq 0.05$

There was no difference in the consumption of propofol, and the doses of propofol used for anesthetic induction were 4.14 ± 1.6 mg/kg in the GK and 5.4 ± 2.7 mg/kg in the GAK.

While evaluating the clinical parameters during the transoperative period for values in the basal measurement, differences were observed at some time points (Table. 4). In the GK, the HR showed a statistical difference at moments M5 (188 ± 37 bpm) and M1 (140 ± 32 bpm). In the GAK, the increase in HR was significant at M4, M5 and M6 (184 ± 37 , $189 \pm$

35 and 162 ± 29 bpm, respectively) when compared to that at M1 (126 ± 19 bpm). There were no significant differences in the HR between the groups.

Table 4. Mean values and standard deviations of the clinical parameters of cats premedicated with ketamine, midazolam and methadone (group ketamine [GK]) or with acepromazine, ketamine, midazolam and methadone (group acepromazine [GAK]), assessed through systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), body temperature (T°C) and oxygen saturation (SO₂) at M1 (after induction), M2 (skin incision), M3 (celiotomy), M4 (right ovarian plexus clamping), M5 (left ovarian plexus clamping), M6 (celiorraphy) and M7 (dermorraphy).

Parameter	Group	Measure	M1	M2	M3	M4	M5	M6	M7
HR	GK	Median	140	134	139	176	188 A	173	140
		Standard deviation	32	34	44	40	37	33	32
	GAK	Median	126	110	137	184 A	189 A	162 A	155
		Standard deviation	19	13	42	37	35	29	34
RR	GK	Median	14	12	12	16	13	12	14
		Standard deviation	4	0	3	4	6	4	4
	GAK	Median	15	14	16	17	17	18	19
		Standard deviation	5	5	6	6	8	9	9
SBP	GK	Median	69	76	97	159 A	156 A	109 A	102
		Standard deviation	12	20	35	34	38	33	27
	GAK	Median	81	96	103	160 A	154 A	117 A	107
		Standard deviation	24	34	38	43	49	53	35
T°C	GK	Median	38,5	37,5	37,2	37,1	36,7	36,6	38,5
		Standard deviation	0,6	1,25	1,1	1,0	1,0	0,8	0,6
	GAK	Median	37,9	37,1 A	36,9 A	36,7 A	36,5 A	36,2 A	36,1 A

		Standard deviation	0,7	0,6	0,6	0,7	0,7	0,9	0,7
SO ₂	GK	Median	99	98	98	99	98	98	98
		Standard deviation	1	1	1	1	1	1	1
	GAK	Median	99	98	98	98	98	99	99
		Standard deviation	1	1	1	1	1	1	1

*A: different from M1 after Dunnett's test, $P \leq 0.05$

Regarding respiratory rate and oxygen saturation, there were no statistical differences between the moments of each group and between the groups (Table. 4); these parameters remained stable during the surgical procedure. SBP showed a significant increase in both groups, at M4, M5 and M6 (159 ± 34 , 156 ± 38 and 109 ± 33 mmHg in GK; 160 ± 43 , 154 ± 49 and 117 ± 53 mmHg in GAK), when compared to that at M1; however, there were no significant differences in SBP between the groups (Table. 4). Regarding analgesic fentanyl rescues, in GK, 6/7 animals received fentanyl, whereas in GAK, all animals received fentanyl. All analgesic rescues were performed at M4 and M5. No significant differences were observed in these values between the groups. The temperature values were significantly lower at all times compared to that at M1 in the GAK (37.1 ± 0.6 , 36.9 ± 0.6 , 36.7 ± 0.7 , 36.7 ± 0.7 , 36.2 ± 0.9 and $36.1 \pm 0.7^\circ\text{C}$ at M2, M3, M4, M5, M6 and M7, respectively). There were no significant differences in the temperature values in GK between times as well as the values between groups (Table. 4). The time of extubation after the end of anesthesia was 3.7 ± 1.3 mins in the GK and 5.2 ± 2.6 mins in the GAK; the time to reach a score equal to 0 on the sedation scale was 88 ± 63.9 mins in the GK and 133 ± 39.7 mins in the GAK. There were no significant differences in these values between the groups. However, when analyzing the data on anesthetic release using the Aldrete scale, the GAK showed a longer time compared to the GK (19.7 ± 6.5 mins vs 11 ± 5.9 mins; $P = 0.023$) (Table. 5).

Table 5. Times, in minutes, of extubation, anesthetic release, and sedation score equal to 0, of cats pre-medicated with ketamine, midazolam, methadone (Group GK) or with acepromazine, ketamine, midazolam, methadone (Group GAK).

		Extubation	Anesthetic release	Sedation score = 0
GC	Median	3,7	11,0 A	88,0
	Standard deviation	1,3	5,9	63,9
GAC	Median	5,3	19,7 A	133,3
	Standard deviation	2,6	6,5	39,7

*A: different between groups after t student test, $P \leq 0,05$.

4. Discussion

Preanesthetic protocols containing ketamine are used in cats, especially in the restless ones where physical restraint is difficult (Martins & Fantoni, 2010). Ketamine is a dissociative anesthetic that is usually associated with benzodiazepines or alpha-2 agonists to minimize the animal's stress and its adverse effects (Marjani, Akbarinejad, Bagheri, 2015). Opioids, associated with tranquilizers or sedatives, are also part of these preanesthetic protocols, providing analgesia and adequate sedation for different types of surgeries and veterinary procedures (Killos, Graham, Lee, 2010; Shah, Yates, Hunt, Murrell, 2018; Steagall, Taylor, Brondoni, Luna, Dixon, 2008). In the present study, both protocols produced a suitable level of sedation during the evaluated period, allowing for the patient's smooth manipulation in preparation for OH.

The administration of an opioid with acepromazine, a combination of sedation and analgesia, generally produces a synergistic effect, thereby increasing the intensity of sedation and analgesia of each drug (Hunt, Grint, Taylor, Murrell, 2014; Steagall et al., 2008).

Additionally, the use of this association in preanesthetic would require less consumption of anesthetics during induction and a more peaceful recovery of the patient (Bortolami, Murrell, Slingsby, 2012; Hunt et al., 2014; Pawson & Forsyth, 2010). In the present study, there was no reduction in the consumption of propofol used in anesthetic induction in the group that received acepromazine or an increase in the degree of sedation, although the discharge from anesthesia, of the animals that received this drug, was later. These results may have been influenced by the latency time of the use of acepromazine applied intramuscularly because the peak effect occurs in 30 mins when applied by this route (Rankin, 2015). Similar results were found in cats premedicated with acepromazine or medetomidine, demonstrating the low sedative effect of acepromazine in this specie (Schwarz et al., 2014).

According to a study carried out in cats subjected to elective OH, the methadone used in preanesthetic promoted analgesia for up to 6.5 h after its administration (Fantoni and Garofalo, 2012). In the present study, the significant increase in clinical parameters, indicative of pain during the period of anesthesia, can be explained by the low dose of methadone used (0.3 mg/kg) and the intensity of the pain generated by traction of the ovarian pedicle. Other researchers claim that methadone at a dose of 0.5 mg/kg is effective for both intraoperative and postoperative analgesia for up to 6 h after administration (Shah et al., 2018; Slingsby, Bortolami, Murrell, 2018).

The association of acepromazine with opioids in preanesthetic can cause different adverse effects, such as hypothermia. When using these preanesthetic drugs, associated with general anesthetics and ambient temperature factors, peripheral vasodilation and consequent decrease in body temperature are observed (Bitti et al., 2017; Manfrinate et al., 2009). In the present study, there was significant hypothermia at different times, when compared to that at M1, in the group that received acepromazine.

The latency time after acepromazine administration is relatively long and it produces sedation for at least 2 to 3 h in the most species (Rankin, 2015). A study that associated ketamine with acepromazine found an increase in the duration of action and effects of ketamine (Steagall et al., 2008). In the present study, the GAK had a longer duration of discharge from the anesthetic because the patients recovered later, in the immediate post anesthetic moment.

Rapid anesthetic recovery is directly linked to the drugs implemented in the protocol and a consequent decrease in body temperature (Robertson et al., 2018). Association of acepromazine with different drugs prolongs its effects, contributing to hypothermia, suggesting that this phenomenon may have occurred in the present study, producing a delayed anesthetic release (Rankin, 2015; Steagall et al., 2009).

It is important to emphasize that this work was carried out in females, so there may be a difference when these protocols are used in males, as the hormonal influence between genders can affect the absorption and metabolism of the drugs used (Hart, Eckstein, 1997).

5. Conclusion

The association of acepromazine with ketamine, midazolam and methadone does not increase the sedation scores, but it promotes a decrease in temperature and delays the anesthetic release.

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