Evaluation of cortisol and glycemia levels of dogs anesthetized with sevoflurane and premedicated with either butorphanol or phetidine

Avaliação dos níveis de cortisol e glicemia em cães anestesiados pelo sevofluorano, pré-medicados com butorfanol ou meperidina

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Abstract

The objective of this study was to compare the influence of butorphanol and phetidine as part of the preanesthetic medication, in 20 healthy dogs submitted to experimental orthopedic surgery. Dogs were randomly allocated in two groups: GI, acepromazine and butorphanol (0,05 mg.kg^{-1} and 0,4 mg.kg^{-1}, respectively, i.m.) and, GII, acepromazine and phetidine (0,05 mg.kg^{-1}and 4 mg.kg^{-1}, respectively, i.m.). Anesthesia was induced by administration of propofol (5 mg.kg^{-1}) and maintained by the use of sevoflurane delivered in a 100% oxygen circuit. Plasma concentrations of cortisol and glucose were measured during several surgical procedures: T0, before preanesthetic medication; T1, 20 minutes after preanesthetic medication; T2, at skin incision; T3, at periostal stimulation; and, T4, at skin suture. Concentrations of plasma glucose were not significantly different between the surgical procedures and between the two groups evaluated. Concentrations of plasma cortisol were significantly higher in dogs administered with butorphanol between the surgical procedures of T0 and T3, compared with values for dogs administered with phetidine. These results suggest that phetidine is more adequate to control plasma cortisol in dogs submitted to orthopedic surgery than anesthesia with sevoflurane.
Key words: Anesthesia, opioids, neuroendocrine stress, canine

Resumo

O objetivo deste estudo foi comparar a influência do butorfanol ou meperidina como medicação pré-anestesica nos níveis de cortisol e glicemia em vinte cães submetidos a cirurgia ortopédica experimental. Os cães foram distribuídos em grupos: GI recebeu acepromazina e butorfanol (0,05 mg.kg^{-1} e 0,4 mg.kg^{-1} respectivamente, i.m.) e GII, acepromazina e meperidina (0,05 mg.kg^{-1} e 4 mg.kg^{-1} respectivamente, i.m.). A indução anestésica constou de propofol (5 mg.kg^{-1}) e para a manutenção sevofluorano em 100% de oxigênio. A concentração plasmátca de cortisol e glicose foram mensuradas no momentos: T0 antes da medicação pré-anestésica; T1 – vinte minutos após a medicação pré-anestésica; T2 – incisão de pele; T3 – estimulação periosteal e T4 – sutura de pele. Não houve diferença entre os momentos e grupos na dosagem de glicose. A concentração plasmatica de cortisol foi significativamente maior nos cães que receberam butorfanol entre T0 e T3, comparado com o grupo que recebeu meperidina. Esses resultados sugerem que a meperidina promove maior controle da dosagem de cortisol em cães submetidos a cirurgia ortopédica e anestesiados com sevofluorano
Palavras-chave: Anestesia, opióides, estresse neuroendócrino, caninos

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Introduction

For a long time a search has been made for the utilization of techniques and concepts that will turn anesthesia safe and applicable to the diverse surgical procedures within Veterinary Medicine (SANTOS, 2003), resulting in the usage of various anesthetic protocols and associations during routine surgery (SANTOS et al., 2004). The multifunctional techniques utilized in associations of volatile or intravenous agents, associations of opioids with regional anesthesia have been used with the objective to obtain desired synergic effects characteristic of various drugs and techniques. Within this context, the use of analgesic agents have received an inverse importance with the intent to serve animal well being and reduce the amount of general anesthetic normally provided, resulting in safe anesthesia and a gradual recuperation (SANTOS, 2003).

Butorphanol is an opioid of mixed action that induces agonist effects in kappa (κ) receptors and antagonist effects on mu (μ) receptors; this is very useful since it induces reduced respiratory depression and stimulates intense sedation in dogs and cats during two hours (FANTONI; MASTROCINQUE, 2002). Phetidine is also an opoid that was initially introduced to veterinary practice as a spasmolytic agent; later it's reduced analgesic effect as a complete agonist of μ receptors, being 10 times more potent than morphine with peak of action attained within one hour. The respiratory depression is similar to that of morphine, and in therapeutic doses does not induce significant alterations to the cardiovascular system (CUNHA; CORTOPASSI; MACHADO, 2002; LAREDO et al., 2001).

Sevoflurane was introduced to medicine in 1990 and gained importance in routine human and veterinary anesthesiology because of its blood-gas partition coefficient, which facilitates rapid and secure induction and recuperation; additionally due to its low metabolic rate, sevoflurane does not provoke renal or hepatic lesions (OLIVA, 2002). Further, it is one of the few inhalation drugs that cause reduced alterations of cardiovascular parameters (IBAÑEZ; AULER JUNIOR; FIGUEIREDO, 2002).

Surgical procedures are associated with a complex stress response characterized by neurohormonal, immunological, and metabolic alterations, these being intimately related to the severity of the lesion, duration of surgery, and the clinical status of the patient (MARANA et al., 2003). These responses have induced a wide range of alterations in diverse organs and systems (MASTROCINQUE; FANTONI, 2001), which have resulted in various studies aimed at minimizing or inhibiting these alterations. In an attempt to identify painful processes in animals, various authors have proposed the evaluation of the levels of seric cortisol and plasmatic catecholamine and thereby identifying techniques and safe anesthesia associations relative to the wellbeing and ethics of animals (FOX et al., 1994; MASTROCINQUE, 2005).

Consequently, the objective of this study was to evaluate neuroendocrine stress based the levels of cortisol and glycemia in dogs submitted to orthopedic surgery that were anesthetized with sevoflurane and pre-medicated with butorphanol or phetidine.

Materials and Methods

Animal group distribution and anesthesia

Twenty adult healthy mongrel dogs, of both sex, with weight varying between 14 ± 2,2 kg were used. All dogs demonstrated hematocrit above 35% and elevated plasma proteins (superior than 7 g/dL), were obtained from the kennel of the Veterinary Hospital, Faculdade Integrado, Campo Mourão, PR, and were being utilized during experimental surgical techniques for the correction of patellar luxation.

Dogs were divided into two groups (n=10): Group I (GI) and Group II (G II). Butorphanol[6] was administered at 0.4 mg kg^{-1} to GI animals, while G II dogs received 4 mg kg^{-1} of phetidine[7] administered

[6] Torbugesic – FortDodge – Campinas, SP.
[7] Dolosal – Cristália – Itapira, SP.

in a study of blind double entry. In both groups, acepromazine[8] was associated in the same syringe that contained either butorphanol or acepromazine, and was administered intramuscularly.

After 20 minutes the cephalic vein of each dog was canalized and an infusion of Ringer Lactate solution (10 mL.kg.hr) was administered throughout the surgical procedure. Anesthetic induction was established with propofol[9] (5 $mg.kg^{-1}$) by the intravenous route. After orotracheal intubation, anesthesia was maintained with sevoflurane[10] in 100% oxygen chamber within a reinalation circuit. During each moment rectal temperature and cardiac and respiratory frequency were evaluated.

Evaluation of glycemia and cortisol

Samples for the evaluation of serum glycemia and plasmatic cortisol were obtained in the following times: T0, before the administration of preanesthetic medication, PAM (control values); T1, 20 minutes after administration of PAM; T2, 20 minutes after T1 in the moment of skin incision; T3, at stimulation of periostal bone; and T4, during skin suture.

Blood samples for glycemia determination were collected from a pre-fixed catheter within the jugular vein, placed in test tubes containing potassium flourate and centrifuged at 3000 rpm during 3 minutes. Determination of seric glycemia was realized with the Glicose PAP – liquiform[11] commercial kit by colorimetric evaluation within an automatic biochemical analyzer[12].

Blood samples for cortisol determination were collected from a pre-fixed catheter within the jugular vein, then placed in test tubes without anticoagulant, centrifuged at 3000 rpm during 3 minutes and maintained at –20 ºC until usage. Cortisol was determined by a Chemiluminescent Enzyme Immunoassay commercial kit[13].

Statistical analyses

All original data were analyzed by computerized software (Minitab14) and submitted to the Normality test; those data that demonstrated normal distribution were analyzed by the Tukey test, while those with abnormal distribution were evaluated with the distribution by the Mann-Whitney test.

Results

Duration of anesthesia was determined by the amount time to apply PAM and needed to finish the surgical procedure. Mean duration for the GI was 88 ± 9,8 minutes and GII 92 ± 10 minutes.

The values of glycemia for dogs anesthetized with sevoflurane and pre-medicated with butorphanol (GI) only demonstrated statistical significant differences ($p < 0.05$) between T0 (before the administration of PAM) and T1 (20 minutes after administration of PAM) in dogs. However this increase in average values was gradual during the other surgical procedures evaluated (Table 1) and was more elevated at T4 (skin suture); these values were within physiological parameters for dogs.

Significant statistical differences ($p > 0.05$) in the level of glycemia were not observed (Table 1) between the surgical procedures in dogs anesthetized with sevoflurane and pre-medicated with phetidine (GII), but the numeric values of cortisol were increased progressively from the first to the last surgical intervention evaluated. When the two groups were compared, significant differences ($p > 0.05$) were observed at T1 in both groups of animals

[8] Acepran 0.2 % – Univet – São Paulo, SP.
[9] Propovan – Cristália – São Paulo, SP.
[10] Sevocris – Cristália – São Paulo, SP.
[11] Glicose PAP – liquiform – Labtest Diagnóstica
[12] Modelo Bio 2000, BioPlus, Barueri, SP. Logoa Santa, MG.
[13] Cortisol DPC – MedLab – São Paulo, SP.

(Figure 1); all other surgical procedures did not demonstrate significant results ($p < 0.05$) between the two groups.

Significant differences ($p < 0.05$) in the increase of the average values of seric cortisol were observed during all individual surgical procedures analyzed in GI animals; however, no significant differences ($p > 0.05$) were observed between the surgical procedures of T1 and T2, and those evaluated at T3 and T4. Independent of this variation, an increase in 200% of the average values was observed immediately after administration of the PAM, with the highest values (10,82 µg/dL) being recorded at T4, and being 300% more elevated than the basal values (Table 2); all average values observed were higher than the physiological values (M0).

Table 1. Variations of glycemia (mg/dL) in dogs anesthetized with sevoflurane and pre-medicated with either butorphanol (Group I) or phetidine (Group II) observed during different times of surgery.

Experimental groups	Statistical parameters	Times of Surgery				
		T0	T1	T2	T3	T4
Group I	Variation coefficient	24,85	24,30	21,40	20,68	12,70
	Average values	89,6*	94,33*	96,47	97,17	99,39
	Standard deviation	22,27	22,92	20,65	20,10	12,62
Group II	Variation coefficient	9,85	10,42	11,72	11,89	15,05
	Average values	82,7+	84,91	88,8	96,76	97,83
	Standard deviation	8,15	8,85	10,41	11,50	14,72

T0, before administration of pre-anesthetic medication; T1, 20 minutes after administration of pre-anesthetic medication; T2, skin incision; T3, stimulation of periostal bone; T4, skin suture.
* Statiscal difference in moments;
+ Statistical difference in groups;

Table 2. Variations of cortisol (µg/dL) in dogs anesthetized with sevoflurane and pre-medicated with either butorphanol (Group I) or phetidine (Group II) observed during different times of surgery.

Experimental groups	Statistical parameters	Times of Surgery				
		T0	T1	T2	T3	T4
Group I	Variation coefficient	59,49	45,17	56,21	35,43	34,08
	Average values	2,85*	6,95*	7,44*	9,56*	10,82*
	Standard deviation	1,70	3,14	4,18	3,39	3,69
Group II	Variation coefficient	34,42	29,45	40,49	27,11	27,51
	Average values	1,66*+	2,99*+	2,49*+	8,23	9,07
	Standard deviation	0,57	0,88	1,01	2,23	2,49

T0, before administration of pre-anesthetic medication; T1, 20 minutes after administration of pre-anesthetic medication; T2, skin incision; T3, stimulation of periostal bone; T4, skin suture.
* Statiscal difference in moments;
+ Statistical difference in groups;

The cortisol values of GII animals did not demonstrate significant difference ($p > 0.05$) before T2, but the average values of T1 and T2 were significantly different ($p < 0.05$) from those of T3 and T4 (Table 2). During this group, the average values of cortisol were maintained close to normal values at T1 and T2, with a marked increase of hormone levels to 500% and 600 % at T3 and T4, respectively (Table 2).

Marked similarity between the average levels of glycemia of the two anesthetic procedures (Figure 1) was well demonstrated at T3 (stimulation of periostal bone) and T4 (skin suture); periods that represented the greatest nociceptive stimulation, while differences were observed at the other surgical procedures.

When the average levels of cortisol for the two treatments were compared (Figure 2), significant differences were observed in animals medicated with butorphanol, particularly at T1 and T2; while the average values of cortisol observed at the other surgical procedure were similar for both treatments. At T1 the average values of cortisol observed were considered as extremely significant ($p < 0.0001$), and very significant ($p=0.0046$) at T2 (Figure 2). Significant differences were not observed in the average values of cortisol during the other surgical procedures when the two treatments were compared.

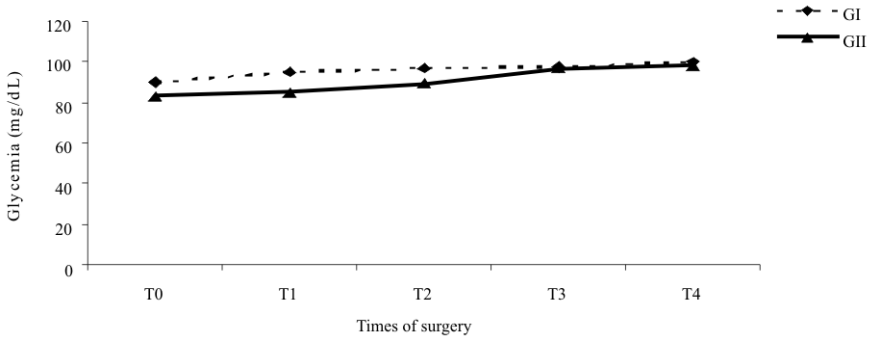

Figure 1. Comparative average values ($\bar{x}$) of glycemia (mg/dL) in dogs anesthetized with sevoflurane and pre-medicated with either butorphanol (GI) or phetidine (GII) during different surgical procedures. (T0, before administration of pre-anesthetic medication; T1, 20 minutes after administration of pre-anesthetic medication; T2, skin incision; T3, stimulation of periostal bone; T4, skin suture).

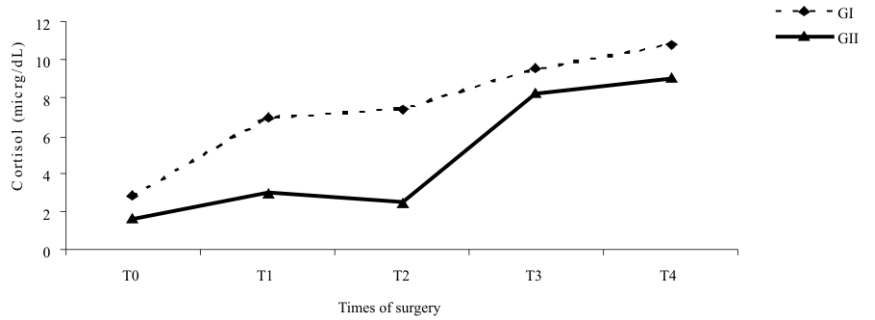

Figure 2. Comparative average values ($\bar{x}$) of cortisol (µg/dL) in dogs anesthetized with sevoflurane and pre-medicated with either butorphanol (GI) or phetidine (GII) during different surgical procedures. (T0, before administration of pre-anesthetic medication; T1, 20 minutes after administration of pre-anesthetic medication; T2, skin incision; T3, stimulation of periostal bone; T4, skin suture).

Discussion

The results from this study have demonstrated that the determination of the levels of gylcemia and cortisol is an efficient method to evaluate nociceptive stimulus in dogs; similar results have been previously described (AMBRISKO; HIKASA; SATO, 2005; KO et al., 2000; MASTROCINQUE; FANTONI, 2001; VAISANEN et al., 2002). The results of the evaluation of cortisol by Chemiluminescent Enzyme Immunoassay were similar to those obtained by others who utilized the radioimmunoassay (AMBRISKO; HIKASA; SATO, 2005; FOX et al., 1994; SOUZA et al., 2001) and floruoimmunoessay (MASTROCINQUE, 2005) techniques in studies realized to evaluate the efficiency of drugs for nociceptive control (FOX et al., 1994; SOUZA et al., 2001); consequently, this method can be considered as adequate and efficient to evaluate the hormone in question.

Although hyperglycemia is the metabolic response to surgical stress, being increased due to an elevation in the levels of cortisol and catecholamine and by the reduced production of insulin (DRUMOND, 2000); the results from this experiment (from both groups) have demonstrated that glycemia was maintained within normal physiological limits for dogs (RIJNBERK; MOL, 1997). However, significant differences were observed in the levels of glycemia for GI animals between the surgical procedures of T0 and T1 (after administration of preanesthetic medication); this ultimate alteration could be related to the stress involved in the contention of animals for the drug administration, similar results have been described (SOUZA et al., 2001) in cats experimentally submitted to ovariohysterectomy and pre-medicated with butorphanol and flunixin meglumin.

Alternatively, these results have demonstrated that phetidine is more efficient to control glycemia and consequently stress at the time of evaluation. However, diverging results were reported (LASCELLES; WATERMAN, 1997; SANO et al., 2003) these authors have indicated that butorphanol has a potent sedative action that is more expressive than other agents of the same pharmacological class. Although the average values of glycemia were maintained within physiological limits (Table 1), the gradual increase in average values demonstrates the inefficiency of both drugs (phetidine and butorphanol) to control the excess to release of cortisol, principally during the periods of intense painful stimulation, characterized by the surgical procedures of T3 and T4.

The use of serum cortisol has been recognized as one of the most efficient methods to evaluate pain in small animals (SMITH; ALLEN; QUANDT, 1999; SOUZA et al. 2001) and humans (EROGLU et al., 2003; GÊISER et al., 2003), and is therefore of importance to evaluate the analgesic efficiency of different drugs. The metabolic response of the organism is influenced by the type of tissue damage induced (MARANA et al., 2003). In experimentally study realized in dogs that were submitted to different surgical procedures and systemic diseases and anesthetized by thiopental and halothane (CHURCH et al., 1994), it was concluded that the act of anesthesia by itself caused an increase in the levels of cortisol; even though all other situations demonstrated increase in plasmatic cortisol. Similar results were related when ovariohysterectomy was used as nociceptive stimulation associated with anesthesia based on protocols with acepromazine, propofol and isoflurane (MASTROCINQUE, 2005), during which it was suggested that the increase in cortisol was due to only anesthesia, even though statistical differences were not observed. The results from this study were similar to those previously described, since not withstanding the anesthetic association, a gradual increase in plasmatic cortisol was observed. During experiments in humans of pelvic laparoscopy (MARANA et al., 2003) and abdominal surgeries (GÊISER et al., 2003), sevoflurane was considered responsible for the increase in cortisol levels as well as other catecholamines, since the group treated with isoflurane demonstrated lower levels than these substances.

During all surgical procedures evaluated during this study, the average values of cortisol and glycemia of GI animals was higher than those observed in their GII counterparts, with significant differences being demonstrated between T0 and T1. Similar results were recently describe in cats (SOUZA et al., 2002), but the variations in serum cortisol observed after the administration of pre-medicated anesthesia were associated with the proximity of unknown individuals, the hospital environment and contention for blood collection. However, these results were different from those related in another study realized in cats where butorphanol and medetomidine was used as PAM (ANSHA et al., 2002); these authors described higher levels of sedation in the group of animals treated with butorphanol, and considered this drug as an excellent option for tranquilization. The increases observed at T2 during this study can be associated with orotracheal intubation; similar results were described (MASTROCINQUE; FANTONI, 2001), but it must be highlighted that phetidine was more efficient in the control of cortisol elevations at the determined surgical procedure.

The results of this evaluation during the diverse surgical procedures realized in GI animals are similar to those previously described (PIBAROT et al., 1997); these authors have indicated that better analgesic efficiency was obtained with ketoprofen relative to butorphanol in the control of post-operative pain due to somatic stimulation. Although post-operative evaluation was not the principal objective of this study exorbitant values of cortisol were observed after extensive nociceptive stimulation, which increased gradually until the last surgical procedure; similar results were described (FANTONI; MASTROCINQUE, 2002; LAREDO et al., 2001; THURMON; TRANQUILLI; BENSON, 1996), where this drug was considered efficient to control visceral pain.

Although phetidine did not induce adequate analgesia to maintain levels of cortisol within physiological values, this agent was more efficient than butorphanol. Similar results were described in an experiment realized in cats submitted to fracture repair and pre-medicated with phetidine and morphine (CUNHA; CORTOPASSI; MACHADO, 2002). Additionally, in an experiment where bitches were submitted to ovariohysterectomy to evaluate the control of anterior sensibilization of the central nervous system to pain with phetidine administered at 5 $mg.kg^{-1}$ (LASCELLES et al., 1997), it was concluded that this drug was effective to control central sensibilization and consequently trans and post-operative pain.

Conclusion

Based on the results obtained from the experiment herein described, it has been concluded that:

Butorphanol administered at 0.4 $mg.kg^{-1}$was not effective to control trans-operative stress based on cortisol and glycemia levels during orthopedic surgery;

Phetidine administered at 4 $mg.kg^{-1}$was more effective in the control of trans-operative neuroendocrine stress, as demonstrated by the levels of glycemia and cortisol, than butorphanol.

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