pubvet
MEDICINA VETERINÁRIA E ZOOTECNIA
ISSN 1982-1263
https://doi.org/10.31533/pubvet.v17n02a1348

Fentanyl for co-induction of propofol anesthesia in dogs premedicated with morphine

Anna Julia Rodrigues Peixoto[1], Matheus Fernandes de Souza[1], Clarice Gonring Corrêa[1], Maria Eduarda dos Santos Lopes Fernandes[1], Viviane Gomes Horta[2*], Cássia Maria Molinaro Coelho[3], Marta Fernanda Albuquerque da Silva[3]

[1]Pós-graduando em Medicina Veterinária, Universidade Federal Rural do Rio de Janeiro (UFRRJ), Departamento de Medicina e Cirurgia Veterinária, Seropédica – RJ, Brasil.
[2]Docente Externo, UFRRJ, Departamento de Medicina e Cirurgia Veterinária, Seropédica – RJ, Brasil.
[3]Professor da UFRRJ, Departamento de Medicina e Cirurgia Veterinária, Seropédica – RJ, Brasil.
**Autor para correspondência, E-mail: viviane.horta@uol.com.br*

Abstract. The aim of the present study was to evaluate the effectiveness of fentanyl to reduce the induction dose of propofol, and to evaluate the quality of induction in dogs premedicated with morphine. The sedative effect promoted by morphine and its action on some physiological variables were also investigated. Twenty-two healthy dogs had their baseline values (BL) of the physiological variables and the degree of sedation recorded. Then, received morphine (0.3 mg/kg) intramuscularly. Ten minutes after morphine administration (T10), all variables were reassessed. Dogs were randomly assigned to intravenously receive fentanyl (2.5 µg/kg) or saline solution (3.0 mL), followed by propofol (2 mg/kg/minute) - groups FP and SP, respectively. The dose of propofol required for intubation and the quality of anesthesia induction were recorded. Morphine administration resulted in vomiting and no sedation. Heart rate significantly decreased at T10 in the FP and SP groups, in relation to BL. The total dose of propofol used for anesthesia induction was 6.4 ± 1.7 and 5.8 ± 1.6 [mean ± standard deviation] mg/kg in FP and SP, respectively, with no differences between groups (P > 0.05). Fentanyl was not effective in reducing the propofol required in the anesthesia induction of dogs premedicated with morphine. Induction was excellent in both groups and may be accompanied by apnea and muscle stiffness. Morphine resulted in no sedation, minimal changes in physiological parameters and vomiting.

Keywords: Anesthesia, canine, co-induction, opioid, sedation

Fentanil para co-indução de anestesia com propofol em cães pré-medicados com morfina

Resumo. O objetivo do presente estudo foi avaliar a capacidade do fentanil em reduzir a dose de indução de propofol e a qualidade da indução em cães pré-medicados com morfina. O efeito sedativo promovido pela morfina e sua ação sobre algumas variáveis fisiológicas também foram investigados. Vinte e dois cães saudáveis tiveram seus valores basais (BL) das variáveis fisiológicas e o grau de sedação registrados. Em seguida, receberam morfina (0,3 mg/kg) por via intramuscular. Dez minutos após a administração da morfina (T10), todas as variáveis foram reavaliadas. Os cães foram aleatoriamente designados a receber por via intravenosa: fentanil (2,5 µg/kg) ou solução salina (3,0 mL), e em seguida propofol (2 mg/kg/minute), grupos FP e SP, respectivamente. A dose de propofol necessária para a intubação e a qualidade da indução foram registradas. A morfina resultou em vômitos e ausência de sedação. A frequência cardíaca diminuiu em T10 nos grupos FP e SP, comparado ao BL. A dose de propofol para indução anestésica foi 6,4 ± 1,7 e 5,8 ± 1,6

[média ± desvio padrão] mg/kg em FP e SP, respectivamente, sem diferenças entre os grupos (P > 0,05). A qualidade de indução anestésica foi excelente em todos os grupos. O fentanil não reduziu o requerimento propofol na indução anestésica de cães pré-medicados com morfina. A indução anestésica foi excelente em ambos os grupos, acompanhada de apneia e rigidez. A morfina resultou em ausência de sedação, alterações mínimas nos parâmetros fisiológicos e vômito.

Palavras-chave: Anestesia, canino, co-indução, opioide, sedação

Introduction

Propofol is a general anesthetic commonly used for induction of anesthesia in dogs (Aguilera et al., 2020; Sánchez et al., 2013; Santos et al., 2012; Souza et al., 2022). The dose of propofol required for orotracheal intubation in dogs ranges from 3 to 10 mg/kg, being influenced by the physical status of the animal and the use or not of premedication (Berry, 2015). Hypotension, respiratory depression and apnea are the most common side effects associated with propofol administration (Miller et al., 2006). During anesthetic induction, other drugs can be used as co-inductors, with the aim of decreasing the required dose of propofol (Covey-Crump & Murison, 2008; Hopkins et al., 2014).

Fentanyl is a full μ-receptor agonist administered intravenously, as a bolus or infusion. The dose of this opioid in dogs ranges from 5 a 10 μg/kg (KuKanich et al., 2005). Few studies have carried out this investigation, but it is known that the use of fentanyl as a co-inductor results in a reduction in the dose of propofol (Covey-Crump & Murison, 2008).

The aim of the present study was to evaluate the effectiveness of fentanyl to reduce the induction dose of propofol and the quality of induction in dogs premedicated with morphine (0.3 mg/kg). The sedative effect promoted by morphine and its action on some physiological variables were also investigated.

Material and methods

The present study was carried out at the Dog and Cat Birth Control Program of the Federal Rural University of Rio de Janeiro (UFRRJ) and was approved by the local animal use committee (nº 3038150915). Twenty-two healthy (American Society of Anesthesiologists class I) male dogs, scheduled for elective orchiectomy, after written consent from all owners, were included in the study. Aggressive or obese dogs were excluded.

All dogs were admitted to the Dog and Cat Birth Control Program of the UFRRJ on the morning of the surgery, fasting for 12 hours of food and 4 hours of water. The dog was acclimatized inside individual kennels located in a quiet room for at least 20 minutes before the start of the study. After acclimatization, baseline values (BL) of heart rate (HR) (by auscultation), systolic arterial pressure (SAP) (by Doppler ultrasonic), respiratory rate (RR) (by observation of thoracic expansion), rectal temperature (RT) (using a digital thermometer) and degree of sedation were recorded. The degree of sedation was assessed using a score from 0 to 3: with 0, no sedation (alert and very responsive to stimuli); 1, mild sedation (quiet but responsive when stimulated); 2, moderate sedation (quiet, reluctant to move, but able to walk); and 3, intense sedation (sleep if not stimulated; unable to walk) (Amengual et al., 2013). Subsequently, the dog received morphine (0.3 mg/kg) intramuscularly (semimembranosus muscle) and returned to its kennel. The occurrence of any side effects of morphine administration was recorded.

Ten minutes after morphine administration HR, SAP, RR, RT and degree of sedation were reassessed. Then, a catheter (XX) suitable for the size of the animal was placed aseptically into a cephalic vein for drug and fluid administration. Dogs were randomly assigned to receive intravenously (IV) one of two treatments (n = 11): fentanyl-propofol (FP group) or saline-propofol (SP group). Fentanyl (2.5 μg/kg diluted in 3.0 mL) (Fentanest® 50 μg/mL) and saline (3.0 mL) (sodium chloride 0.9%®) were administered over 45 seconds. Immediately after administration of the co-induction agent, anesthesia was induced with propofol (2 mg/kg/minute) (Propovan® 10 mg/mL) as needed to allow endotracheal intubation, characterized by loss of consciousness, jaw tone and lateral eyelid reflex. The dose of propofol required for intubation was recorded for each dog.

The quality of anesthetic induction was assessed using a scoring system from 1 to 4: with 1, excellent (no excitement, pedaling, vocalization, tremors or vomiting); 2, good (minimal excitement, some head movement, slight tremors but no pedaling, vocalization or vomiting); 3, regular (moderate excitement, light pedaling, vocalization, tremors or vomiting); and 4, bad (intense excitement, aggression, vocalization, violent movements, or convulsion; rescue sedation required) (Psatha et al., 2011). During anesthetic induction, the occurrence of excitation, muscle stiffness and apnea was recorded.

Statistical analysis was performed using SigmaPlot Version 11.0 (Systat Software Inc., CA, USA). The Shapiro–Wilk test was used to assess normal distribution of the variables. Differences between groups, and between BL and T10 times were determined using a t-test and the Mann–Whitney. For all analyses, values of $P < 0.05$ were considered significant.

Results

Twenty-two healthy male dogs included in the study, aged 2 and 8 years, weighing 17.0 ± 7.1 (9–31) kg [mean ± standard deviation (range)].

Morphine administration resulted in vomiting in eight dogs, four each group. At T10, one dog in the fentanyl-propofol and two dogs in the saline-propofol showed mild sedation. All other dogs showed no signs of sedation at T10. There was no difference in the degree of sedation between T10 and BL ($P > 0.05$) (Table 1). HR decreased from BL at T10 in FP ($P = 0.015$) and in SP ($P = 0.003$) (Table 1). Degree of sedation, HR, SAP, RR and RT were not different between treatments ($P > 0.05$) (Table 1).

Table 1. Degree of sedation, heart rate (HR), systolic arterial pressure (SAP), respiratory rate (RR) and rectal temperature (RT) in 22 dogs (*n* = 11 dogs per group) at baseline (BL) and 10 minutes after muscle administration of morphine (0.3 mg/kg) intramuscularly (T10).

Variables	Treatments	Baseline values (BL)	Ten minutes after morphine administration (T10)
Degree of sedation (0–3)	Fentanyl-propofol	0 (0–0)	0 (0–1)
	Saline-propofol	0 (0–0)	0 (0–1)
HR (beats minute^{-1})	Fentanyl-propofol	107 ± 15	95 ± 12*
	saline-propofol	109 ± 16	99 ± 12*
SAP (mmHg)	Fentanyl-propofol	155 ± 29	164 ± 23
	Saline-propofol	156 ± 40	152 ± 31
RR (breaths minute^{-1})	Fentanyl-propofol	36 ± 2	35 ± 1
	Saline-propofol	38 ± 1	32 ± 3
RT (Cº)	Fentanyl-propofol	39.1 ± 0.5	38.9 ± 0.5
	Saline-propofol	39.4 ± 0.4	39.2 ± 0.4

Sedation score showed as median (minimum-maximum). HR, SAP, RR, RT showed as mean ± standard deviation. *Significant difference from baseline within the same treatment.

There was no difference between the groups regarding the total dose of propofol used for anesthetic induction ($P = 0.401$) and the quality of anesthetic induction ($P = 0.581$) (Table 2). The quality of anesthetic induction score was 1 (excellent) in all groups (Table 2). During anesthetic induction, no animal showed excitement, seven dogs in FP group and six the SP group showed apnea, two dogs in FP group showed muscle stiffness.

Table 2. Total dose of propofol used for anesthetic induction and quality of anesthetic induction in 22 dogs (*n* = 11 dogs per group) premedicated with morphine (0.3 mg/kg) intramuscularly.

Treatments	Total dose of propofol (mg/kg)	Quality of anesthetic induction scores (1–4)
Fentanyl-propofol	6.4 ± 1.7	1 (1–2)
Saline-propofol	5.8 ± 1.6	1 (1–2)

Discussion

The administration of fentanyl (2.5 µg/kg) was not effective in reducing the propofol requirement in the anesthetic induction of dogs premedicated with morphine (0.3 mg/kg). Anesthetic induction was classified as excellent in all groups. After 10 minutes of morphine administration, no sedation was observed and changes in physiological parameters observed were minimal. The limitation of this study is the lack of statistical methods of sample size or power calculation, which impairs the reliability of the results.

To date, few studies have investigated the sedative effects of morphine alone (Maiante et al., 2009), but it is known that this opioid alone in dogs, induces mild to moderate sedation (Maiante et al., 2009; Mich & Hellyer, 2008). However, in the present study 86% of the dogs showed no signs of sedation after morphine administration. This result can be explained by the dose of morphine used, the moment of sedation assessment (only 10 minutes after administration), the number and experience of observers assessing sedation and individual variation of the animals. No studies were found comparing the sedation produced by different doses of morphine alone.

In the present study 36% of dogs vomited after morphine (0.3 mg/kg) administration. This side effect is mediated by the action of morphine, which stimulates the δ receptors in the chemoreceptor trigger zone (CTZ) (Blancquaert et al., 1986). Previous studies have observed vomiting in 75% of dogs that received 0.5 mg/kg morphine intramuscularly (Valverde et al., 2004).

In the present study, after the administration of morphine, a decrease in heart rate was observed, without the occurrence of bradycardia. This result is mediated by the increase in vagal tone promoted by opioids (Aleixo & Tudury, 2007; Ribeiro et al., 2002; Valadão et al., 2002). The results of the present study suggest that the administration of 0.3 mg/kg of morphine is safe, as the HR, SAP, RR and RT values remained within the appropriate range for dogs (Grubb et al., 2020).

In the present study, the doses of propofol used for orotracheal intubation are within the range recommended by the literature (Berry, 2015). The dose of 2 µg/kg of fentanyl was able to reduce the induction dose of propofol (Covey-Crump & Murison, 2008). However, in the present study, when using 2.5 µg/kg of fentanyl, the result obtained was different. Several reasons may justify the ineffectiveness of fentanyl in reducing the dose of propofol in this study, such as the population of dogs used, the sedative effect obtained with premedication, and the rate and method of propofol administration. The quality of induction promoted by the fentanyl-propofol and saline-propofol combination in this study was excellent, a result similar to that observed in previous studies (Covey-Crump & Murison, 2008).

It is known that slow administration of propofol appears to be associated with a lower incidence of apnea in dogs (Murison, 2001), but even when administering this anesthetic slowly, many dogs in this study had apnea. The respiratory depression resulting from the administration of propofol and the depressant effect on the respiratory system of fentanyl are responsible for this result (Berry, 2015; Kotschwar et al., 2009; Stegmann & Bester, 2001). Two dogs that received fentanyl-propofol had muscle rigidity which resolved spontaneously. This occurrence is described in the literature, being usually observed in clinical routine, and its causes are uncertain (Sams et al., 2008).

Conclusion

Fentanyl (2.5 µg/kg) was not able to reduce the propofol induction dose in dogs premedicated with morphine (0.3 mg/kg). The quality of anesthetic induction was excellent, with apnea and muscle stiffness being observed. The 0.3 mg/kg dose of morphine does not result in sedation produces vomiting and minimal effects on HR, SAP, RR and TR.

References

Aguilera, R., Sinclair, M., Valverde, A., Bateman, S., & Hanna, B. (2020). Dose and cardiopulmonary effects of propofol alone or with midazolam for induction of anesthesia in critically ill dogs. *Veterinary Anaesthesia and Analgesia*, *47*(4), 472–480. https://doi.org/10.1016/j.vaa.2020.03.006.

Aleixo, G. A. S., & Tudury, E. A. (2007). Utilização de opióides na analgesia de cães e gatos. *Veterinária Notícias*, *11*(2), 31–42.

Amengual, M., Flaherty, D., Auckburally, A., Bell, A. M., Scott, E. M., & Pawson, P. (2013). An evaluation of anaesthetic induction in healthy dogs using rapid intravenous injection of propofol or alfaxalone. *Veterinary Anaesthesia and Analgesia*, *40*(2), 115–123. https://doi.org/10.1111/j.1467-2995.2012.00747.x.

Berry, S. H. (2015). Analgesia in the perioperative period. In L. S. Waddell (Ed.), *Veterinary Clinics of North America: Small Animal Practice - Perioperative Care* (pp. 1013–1027). https://doi.org/10.1016/j.cvsm.2015.04.007.

Blancquaert, J.-P., Lefebvre, R. A., & Willems, J. L. (1986). Emetic and antiemetic effects of opioids in the dog. *European Journal of Pharmacology*, *128*(3), 143–150. https://doi.org/10.1016/0014-2999(86)90760-0.

Covey-Crump, G. L., & Murison, P. J. (2008). Fentanyl or midazolam for co-induction of anaesthesia with propofol in dogs. *Veterinary Anaesthesia and Analgesia*, *35*(6), 463–472. https://doi.org/10.1111/j.1467-2995.2008.00408.x.

Grubb, T., Sager, J., Gaynor, J. S., Montgomery, E., Parker, J. A., Shafford, H., & Tearney, C. (2020). 2020 AAHA anesthesia and monitoring guidelines for dogs and cats. *Journal of the American Animal Hospital Association*, *56*(2), 59–82. https://doi.org/10.5326/JAAHA-MS-7055.

Hopkins, A., Giuffrida, M., & Larenza, M. P. (2014). Midazolam, as a co-induction agent, has propofol sparing effects but also decreases systolic blood pressure in healthy dogs. *Veterinary Anaesthesia and Analgesia*, *41*(1), 64–72. https://doi.org/10.1111/vaa.12088.

Kotschwar, J. L., Coetzee, J. F., Anderson, D. E., Gehring, R., KuKanich, B., & Apley, M. D. (2009). Analgesic efficacy of sodium salicylate in an amphotericin B-induced bovine synovitis-arthritis model. *Journal of Dairy Science*, *92*(8), 3731–3743. https://doi.org/10.3168/jds.2009-2058.

KuKanich, B., Lascelles, B. D. X., & Papich, M. G. (2005). Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *28*(4), 371–376. https://doi.org/10.1111/j.1365-2885.2005.00661.x.

Maiante, A. A., Teixeira Neto, F. J., Beier, S. L., Corrente, J. E., & Pedroso, C. (2009). Comparison of the cardio-respiratory effects of methadone and morphine in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *32*(4), 317–328. https://doi.org/10.1111/j.1365-2885.2008.01042.x.

Mich, P. M., & Hellyer, P. (2008). Objective, categoric methods for assessing pain and analgesia. In J. S. Gaynor & W. W. Muir (Eds.), *Handbook of veterinary pain management* (pp. 78–109). https://doi.org/10.1016/B978-032304679-4.10006-1.

Miller, P., Mack, C. D., Sammer, M., Rozet, I., Lee, L. A., Muangman, S., Wang, M., Hollingworth, W., Lam, A. M., & Vavilala, M. S. (2006). The incidence and risk factors for hypotension during emergent decompressive craniotomy in children with traumatic brain injury. *Anesthesia & Analgesia*, *103*(4), 869–875. https://doi.org/10.1213/01.ane.0000237327.12205.dc.

Murison, P. J. (2001). Effect of propofol at two injection rates or thiopentone on post-intubation apnoea in the dog. *Journal of Small Animal Practice*, *42*(2), 71–74. https://doi.org/10.1111/j.1748-5827.2001.tb01995.x.

Psatha, E., Alibhai, H. I. K., Jimenez-Lozano, A., Armitage-Chan, E., & Brodbelt, D. C. (2011). Clinical efficacy and cardiorespiratory effects of alfaxalone, or diazepam/fentanyl for induction of anaesthesia in dogs that are a poor anaesthetic risk. *Veterinary Anaesthesia and Analgesia*, *38*(1), 24–36. https://doi.org/10.1111/j.1467-2995.2010.00577.x.

Ribeiro, S., Schmidt, A. P., & Schmidt, S. R. G. (2002). O uso de opióides no tratamento da dor crônica não oncológica: o papel da metadona. *Revista Brasileira de Anestesiologista*, *52*(5), 644–651.

Sams, L., Braun, C., Allman, D., & Hofmeister, E. (2008). A comparison of the effects of propofol and etomidate on the induction of anesthesia and on cardiopulmonary parameters in dogs. *Veterinary Anaesthesia and Analgesia*, *35*(6), 488–494. https://doi.org/10.1111/j.1467-2995.2008.00417.x.

Sánchez, A., Belda, E., Escobar, M., Agut, A., Soler, M., & Laredo, F. G. (2013). Effects of altering the sequence of midazolam and propofol during co-induction of anaesthesia. *Veterinary Anaesthesia and Analgesia*, *40*(4), 359–366. https://doi.org/10.1111/vaa.12038.

Santos, A. L. Q., Oliveira, S. R. P., Kaminishi, A. P. S., Andrade, M. B., Menezes, L. T., Souza, R. R., Ferreira, C. H., Nascimento, L. R., & Moraes, F. M. (2012). Avaliação do uso da combinação de propofol e midazolam na contenção farmacológica e anestesia do cágado-de-barbicha Phynops geoffroanus Schweigger, 1812 (Testudines, Chelidae). *PUBVET*, *6*(12), 1331–1337. https://doi.org/10.22256/pubvet.v16n12.1337.

Souza, M. F., Peixoto, A. J. R., Corrêa, C. G., Fernandes, M. E. S. L., Oliveira, J., Gomes, V. H., Coelho, C. M. M., & Silva, M. F. A. (2022). Midazolam ou fentanil para co-indução de anestesia com propofol em cadelas pré-medicadas com acepromazina-morfina. *PUBVET*, *16*(9), 1–7. https://doi.org/10.31533/pubvet.v16n09a1216.1-7.

Stegmann, G. F., & Bester, L. (2001). Some clinical effects of midazolam premedication in propofol-induced and isoflurane-maintained anaesthesia in dogs during ovariohysterectomy. *Journal of the South African Veterinary Association*, *72*(4), 214–216. https://doi.org/10.4102/jsava.v72i4.655.

Valadão, C. A. A., Duque, J. C., & Farias, A. (2002). Administração epidural de opióides em cães. *Ciência Rural*, *32*(2), 347–355.

Valverde, A., Cantwell, S., Hernández, J., & Brotherson, C. (2004). Effects of acepromazine on the incidence of vomiting associated with opioid administration in dogs. *Veterinary Anaesthesia and Analgesia*, *31*(1), 40–45. https://doi.org/10.1111/j.1467-2995.2004.00128.x.

Article History:
Received: February 6, 2023
Accepted: February 13, 2023