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Cardiopulmonary and sedative effects of intravenous or epidural methadone in conscious dogs

Cardiopulmonary and sedative effects of intravenous or epidural methadone were compared. Six beagles were randomly assigned to group MIV (methadone 0.5 mg kg^{-1} IV + NaCl 0.9% epidurally) or MEP (methadone 0.5 mg kg^{-1} epidurally + NaCl 0.9% IV). Cardiopulmonary, blood gas and sedative effects were assessed at time (T) 0, 15, 30, 60, 120, 240 and 480 minutes after drug administration. Compared to T0, heart rate decreased at T15 - T120 in MIV ($p<0.001$) and T15 - T240 in MEP ($p<0.05$); mean arterial pressure was reduced at T15 - T60 in MEP ($p<0.01$); respiratory rate was higher at T15 and T30 in both groups ($p<0.05$); pH was lower at T15 - T120 in MIV ($p<0.01$) and T15, T30 and T120 in MEP ($p<0.05$); $PaCO_2$ was higher at T15 - T60 in MIV ($p<0.01$) and T15, T30 and T120 in MEP ($p<0.01$); sedation scores were higher at T15 and T30 in MIV and T15 – T60 in MEP ($P < 0.05$). At T120 and T240, sedation score was higher in group MEP compared with group MIV ($P < 0.01$) In conclusion, cardiopulmonary and sedative effects of identical doses of methadone are similar when administered IV or epidurally in conscious healthy dogs.

Key words: cardiorespiratory, dog, extradural, opioids, sedation.

Epidural (EP) administration of opioids provides better antinociceptive effects, with apparent minimal influence on cardiorespiratory function compared with other routes of administration (Pascoe, 2000). Furthermore, lower doses are required and the duration of antinociception is longer compared with administration by other parenteral routes (Valverde et al., 1992). However, these advantages are associated with EP administration of principally morphine. Methadone is a synthetic opioid analgesic with additional anti-nociceptive properties and when administered EP appears to result in fewer adverse effects than morphine when

administered epidurally to women undergoing obstetrical procedures (Beeby et al., 1984). Nevertheless, it has been suggested that there is little advantage in the administration of EP methadone due to its lipophilic nature – its duration of action is not prolonged and there is significant systemic uptake (Davis & Walsh, 2001). The purpose of this study was to compare the sedative and cardiopulmonary effects of methadone given IV or EP to healthy, conscious dogs, during eight hours of assessment.

This research was conducted under the approval of the Institutional Ethics Committee on Animal Care protocol number 032/13. Six beagle dogs (4 male and 2 female), all 2 years old, weighing 15.3 ± 2.2 kg were used in this study. Healthy status was confirmed following physical examination, complete blood count and serum analysis of renal and liver function. The animals were conditioned for 30 days prior to initiation of the study. Immediately prior to each part of the study, animals were fasted for 8 hours and water was restricted for 4 hours.

The dogs were selected to receive one of 2 treatments in random order in a crossover design with a minimum interval of 7 days between treatments. Group MIV received 0.5 mg/kg methadone (Metadon, Critstália, Itapira, Brazil) IV and normal saline (Fisiológico, JP Indústria Farmacêutica S.A., Ribeirão Preto, Brazil) EP via epidural catheter; group MEP received 0.5 mg/kg methadone EP via epidural catheter and normal saline IV. Epidural and IV administration of methadone and saline was performed simultaneously. The final volume of injected in both groups, epidurally or IV was 0.4 mL/kg, adjusting when necessary with normal saline solution. Sedation scores, cardiopulmonary and blood gas measurements and body temperature, were recorded before drug administration (baseline or T0), and 15, 30, 60, 120, 240 and 480 minutes following drug administration (T15 – T480).

Epidural catheter (Becton Dickinson, BD™ Catheter Epidural, São Paulo, SP, Brazil) placement was performed at the lumbosacral intervertebral space using a technique described by Valverde (2008). Dogs were anaesthetised using propofol administered IV (Propovan,

Cristália, Brazil) (mean dose was 10 mg/kg IV). Anaesthesia was maintained by administering further incremental propofol to effect as necessary (incremental dose 1 mg/kg). During this period, pulse rate, respiratory rate (f_R) and haemoglobin oxygen saturation (SpO_2) were monitored with a pulse oximeter. If the $SpO_2 \leq 95$, the trachea was intubated with an endotracheal tube and/or oxygen supplementation was carried out. Following epidural catheter placement, the animals were allowed to recover completely from anaesthesia until spontaneous ambulation was possible, without any clinical signs of central nervous system depression such as response to voice and touch and interaction with the environment.

Heart rate (HR) was determined by measuring the intervals between R waves by intermittent electrocardiography (TEB® ECGPC software v. 1.1, São Paulo, Brazil) during one minute of analysis; cardiac rhythm was also assessed at this time. Following desensitization of the skin with 1 mL of lidocaine, a 22G x 1" catheter was placed in a dorsal metatarsal artery. The artery was connected to a calibrated aneroid manometer (Bic Med, Itupeva, Brazil) through a line filled with heparin solution (50 IU/mL) and used to measure mean arterial blood pressure (MAP). The system was zeroed at the level of the right atrium (xiphoid process for laterally recumbent animals and the point of shoulder for standing or sternally recumbent animals). Rectal temperature (RT – Celsius degrees °C) was assessed using a clinical thermometer (Flexterm, Incoterm, Porto Alegre, Brazil). Respiratory rate was evaluated by observation of costal movements over one minute. Arterial blood (0.5 mL) was drawn into heparinised syringes for measurement of pH, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), arterial haemoglobin oxygen saturation (SaO_2), base excess (BE), bicarbonate ($[HCO_3^-]$), sodium ($[Na^+]$), potassium ($[K^+]$) and chloride ($[Cl^-]$) ion concentrations. Blood samples were taken from the arterial catheter after discarding the first 2 mL and the syringe was sealed with rubber cap. Arterial blood samples were analysed immediately using an automatic blood gas and electrolyte analyzer (Cobas b 121 Roche®,

Basel, Switzerland). The measurements were corrected according to the patient's body temperature by the analyzer. Sedation was assessed interactively, according to a scale proposed by Kuusela et al. (2000). Three proficient evaluators, blinded to the route of administration of methadone, scored sedation. Changes in posture, eyelid reflex, position of the ocular globe, resistance to adoption of lateral recumbency, mandibular and tongue relaxation, response to hand clapping and overall appearance were used for scoring sedation, which could range from 0 to 20 points (Appendix 1). The final mean score was the arithmetic mean of the three evaluators, which was used for statistical analysis.

Following assessment of normality using the Shapiro-Wilk's test, data were analysed using GraphPad PRISM v. 5 (GraphPad Software, Inc., La Jolla, CA, USA). Repeated measures two-way ANOVA and Bonferroni's post-test were used for comparison of cardiopulmonary variables, rectal temperature and blood gas measurements among time points. To compare between treatments at the same time points, the Student's *t* test was applied. Sedation scores were compared using Friedman's test and Dunn's post-test, if necessary. The level of significance was set at 5%.

The results are shown as mean ± standard deviation (SD), for parametric data and as a median (range) for non-parametric data. There were no complications during insertion of the epidural catheter. The hanging drop test was positive in all animals, which allowed for the determination of the correct placement of the Tuohy needle and total time for complete procedure insertion was 14.7 ± 4 minutes.

Cardiopulmonary data are shown in Table 1. There were no significant differences between treatments at any time point ($P > 0.05$). There was a decrease in HR from T15 - T120 in MIV ($P < 0.001$) and T15 - T120 ($P < 0.001$) and T240 ($P < 0.05$) in MEP, when compared to baseline. No changes in cardiac rhythm occurred over the period of evaluation. In group MEP, a significant decrease in MAP occurred at T15 - T60 ($P < 0.01$). Compared with

baseline, f_R was significantly increased at T15 and T30 in group MIV ($P < 0.01$), and at T15 and T30 in group MEP ($P < 0.05$). Compared with baseline, RT was significantly decreased in group MIV at T30 - T120 ($P < 0.05$) and in group MEP at T15 ($P < 0.05$), T30 ($P < 0.01$) and, T60 - T240 ($P < 0.001$).

Compared with baseline, mean pH values were significantly decreased at T15 - T60 ($P < 0.001$) and T120 ($P < 0.01$) in group MIV, and at T15, T30 and T120 in group MEP ($P < 0.05$). $PaCO_2$ was significantly increased at T15, T30 ($P < 0.01$) and T60 ($P < 0.001$) in group MIV, and at T15, T30 and T120 in group MEP ($P < 0.01$), compared with baseline. There were no significant differences in PaO_2 and SaO_2. There were no other significant differences between treatments in arterial blood gas and electrolyte measurements at any time point ($P > 0.05$) (Tab. 2).

Sedation scores were higher in comparison with baseline at T15 and T30 in group MIV, and at T15 – T60 in group MEP ($P < 0.05$). At T120 and T240, sedation score was higher in group MEP compared with group MIV ($P < 0.01$) (Tab. 3). Only one animal in group MIV demonstrated clinical signs of central nervous system (CNS) excitation (dysphoria) up to 60 minutes following drug administration. The animal became restless and attempted to jump off the examination table several times. This behaviour was not evident prior to methadone administration.

This study demonstrates that cardiopulmonary and sedative effects are similar when identical doses of methadone are administered IV or EP to healthy, conscious dogs.

Alterations in HR induced by methadone are usually attributed to a direct action on vagal tone (Stanley et al. 1980). Additionally, a baroreceptor-mediated fall in HR has been described in response to vasoconstriction and increased systemic vascular resistance and MAP (Hellebrekers et al., 1989; Maiante et al., 2009). This increase in blood pressure may be a consequence of CNS excitation (Maiante et al., 2009) or the secretion of arginine vasopressin

(AVP) (Hellebrekers et al., 1989; Maiante et al., 2009). However, we did not observe an increase in MAP following the administration of methadone and cannot corroborate this peripheral effect on HR or on the secretion of AVP; this may be a reflection of the dose of methadone used in our study. In a similar study in isoflurane-anaesthetised dogs, a fall in HR occurred almost immediately (within 1 minute) following IV injection of methadone, whilst such an effect was observed only after 10 - 50 minutes following epidural administration (Campagnol et al., 2012).

In the study documented here, panting occurred for up to 30 minutes following administration of methadone in both treatment groups. This systemic effect of methadone has been described in other studies in conscious dogs (Maiante et al., 2009). It has been suggested that the panting often observed following the administration of μ agonist opioids, particularly to pain-free animals as in this study, may be secondary to changes in the thermoregulatory center and the animal attempting to cool itself down (Pascoe, 2000). Indeed, the rectal temperature of dogs in both treatment groups did fall significantly over time, in agreement with Maiante et al. (2009), which may be attributable to the aforementioned effect on the thermoregulatory center. However, sedation will also induce reduced muscular function, which may lead to a fall in body temperature. Oxygenation appeared to be unaffected despite the reduction in ventilation although PaO_2 did decrease slightly. However, $PaCO_2$ and RT remained within the physiological range and changes were not clinically significant. Nevertheless, these changes are similar between the treatment groups, suggesting significant systemic uptake of methadone from the epidural space.

There appeared to be minimal changes in acid base status, blood gas values and electrolyte concentrations in our study. Arterial pH did decrease following methadone administration in both treatment groups. However, this change in pH can be directly attributed to increases in $PaCO_2$, probably as a consequence of panting, although values for both pH and

$PaCO_2$ remained within the physiological range. Other studies have produced similar findings (Garofalo et al., 2012), although alternative speculative explanations have included the development of a mild metabolic acidosis as a result of reduced tissue perfusion secondary to elevations in AVP concentrations (Hellebrekers et al., 1989; Garofalo et al., 2012). As we did not identify significant changes in $[HCO_3^-]$ or BE, we cannot corroborate this theory.

The systemic absorption of any drug from the EP space is determined in part by its lipophilicity (Valverde, 2008). The lipophilic nature of methadone may explain the similarity of sedation scores observed in this study between treatments. This is in contrast to our hypothesis in which we had anticipated superior sedation following IV administration of methadone. In light of the results presented in this study, it is difficult to recommend the administration of methadone epidurally based upon this assumption, since the level of sedation was the same and the duration of sedation was longer following administration via this route.

A limitation of this study is that we did not assess the analgesic potency of the treatments. Although identical doses of methadone were administered by both routes, it might be expected that analgesia in group MEP would be superior compared to group MIV. As the drug is administered close to the effect site a smaller dose of methadone may produce similar analgesic effects. Furthermore, as doses were identical, the sedative and cardiopulmonary effects are likely to be similar between groups due to systemic absorption of methadone administered epidurally. However, plasma concentrations were not measured and we cannot confirm that this is true. Further studies are warranted to assess the analgesic potency of lower doses of methadone administered by the EP route.

In conclusion, identical doses of methadone administered IV or EP lead to similar cardiopulmonary changes in healthy, conscious dogs with longer effects when administered epidurally.

REFERENCES

Beeby, D., MacIntosh, K.C., Bailey, M. & Welch, D.B. (1984) Postoperative analgesia for caesarian section using epidural methadone. *Anaesthesia*, 39, 61–63.

Campagnol, D., Teixeira-Neto, F.J., Peccinini, R.G., Oliveira F.A., Alvaides, R.K. & Medeiros, L.Q. (2012) Comparison of the effects of peridural or intravenous methadone on the minimum alveolar concentration of isoflurane in dogs. *The Veterinary Journal*, 19, 311–315.

Davis, M.P. & Walsh, D. (2001) Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocol of administration. *Supportive Care in Cancer*, 9, 73–83.

Garofalo, N.A., Teixeira-Neto, F.J., Pereira, C.D., Pignaton, W., Vicente, F. & Alvaides, R.K. (2012) Cardiorespiratory and neuroendocrine changes induced by methadone in conscious and in isoflurane anaesthetized dogs. *The Veterinary Journal,* 194, 398–404.

Hellebrekers, L.J., Van Den Brom, W.E. & Mol, J.A. (1989) Plasma arginine vasopressin response to intravenous methadone and naloxone in conscious dogs. *The journal of Pharmacology and Experimental Therapeutics*, 248, 329–248.

Kuusela, E., Raekallio, M., Anttila, M., Falck, I.; Mölsä, S. & Vainio, O. (2000) Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *Journal of Veterinary Pharmacology and Therapeutics*, 23, 15–20.

Maiante, A.A., Teixeira Neto, F.J., Beier, S.L., Corrente, J.E. & Pedroso, C.E. (2009) Comparison of the cardio-respiratory effects of methadone and morphine in conscious dogs. *Journal of Veterinary Pharmacology and Therapeutics*, 32, 317–328.

Pascoe, P.J. (2000) Opioid analgesics. *Veterinary Clinics of North America Small Animal Practice*, 30, 757–72.

201 Stanley, T.H., Liu, W.S., Webster, L.R. & Johansen, R.K. (1980) Haemodinamic effects of
202 intravenous methadone anaesthesia in dogs. *Canadian Anaesthetists' Society Journal*, 27, 53–
203 57.
204 Valverde, A., Conlon, P.D., Dyson, D.H. & Burger J.P. (1992) Cisternal CSF and serum
205 concentrations of morphine following epidural administration in the dog. *Journal of*
206 *Veterinary Pharmacology and Therapeutics*, 15, 91–95.
207 Valverde, A. (2008) Epidural analgesia and anesthesia in dogs and cats. *Veterinary Clinics of*
208 *North America Small Animal Practice*, 38, 1205–1230, 2008.
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