A comparison of the analgesic efficacy of vedaprofeno, carprofen or ketofen after ovariohysterectomy in bitches

Comparação da eficácia analgésica do vedaprofeno, do carprofeno ou do cetoprofeno após ovariohisterectomia em cadelas

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ABSTRACT

In this study the authors aimed to compare the efficiency of carprofen, ketoprofen and vedaprofen for alleviating postoperative pain in bitches submitted to ovariohysterectomy (OH). Pre- and postoperative assessment of pain was made using serum levels of cortisol and glucose, the visual analogue scale (VAS) and the University of Melbourne pain scale (UMPS) in twenty-one bitches undergoing OH. Dogs were randomly assigned to one of three groups: vedaprofen at 0.5mg kg^{-1}, carprofen at 2.2mg kg^{-1} or ketoprofen at 2.2mg kg^{-1}. All analgesics were given orally 2 hour before surgery. Assessments were made before surgery and at 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours post-extubation. No dog of this study required additional doses of analgesics. There were no significant differences on serum cortisol and glucose concentrations among groups or from basal values, excepted one hour after extubation. No significant differences on pain scores were observed. It was concluded that vedaprofen provided as good a level of postoperative analgesia as carprofen and ketoprofen.

Key words: NSAIDS, analgesia, carprofen, ketoprofen, vedaprofen, ovariohysterectomy, dogs.

RESUMO

O objetivo deste estudo foi comparar a eficiência do carprofeno, do cetoprofeno e do vedaprofeno no alívio da dor pós-operatória em cadelas submetidas à ovariohisterectomia (OH) eletiva. Para tal, foram realizadas avaliações pré e pós-operatórias de cortisol e glicose séricos e foram usadas a escala análoga visual (VAS) e a escala da Universidade de Melbourne (University of Melbourne Pain Scale – UMPS). Vinte e uma cadelas foram distribuídas aleatoriamente em três grupos de sete animais cada: vedaprofeno 0,5mg kg^{-1}, carprofeno 2,2mg kg^{-1} ou cetoprofeno 2,2mg kg^{-1}. Todos os analgésicos foram administrados pela via oral, duas horas antes da cirurgia. As avaliações foram realizadas antes da cirurgia e uma, duas, três, quatro, cinco, seis, sete, oito, 12 e 24 horas após a extubação. Nenhum dos cães precisou de analgesia de resgate. Com exceção dos valores observados uma hora após a extubação, não houve diferenças significativas nas concentrações séricas de cortisol e glicose entre grupos ou quando foram comparadas aos valores basais. Tampouco houve diferenças significativas nos escores de dor entre as escalas usadas, nos tempos de avaliação para cada grupo, nem entre os grupos. Concluiu-se que o vedaprofeno fornece analgesia pós-operatória de qualidade similar à obtida com carprofeno e com cetoprofeno.

Palavras-chave: AINES, analgesia, carprofeno, cetoprofeno, vedaprofeno, ovariohisterectomia, cães.

INTRODUCTION

Several opioids and non-steroidal anti-inflammatory drugs (NSAIDs) are used to provide perioperative analgesia in dogs (FIRTH & HALDANE 1999; GRISNEAUX et al., 1999) and cats (SLINGSBY & WATER-PEARSON, 2000). NSAIDs have been demonstrated to be very effective analgesic agents and have the advantage that they are not controlled drugs (GRISNEAUX et al., 1999). The NSAIDs act by blocking the action of cyclooxygenase (COX), which catalyzes

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the transformation of arachidonic acid into thromboxanes, prostacyclin, and prostaglandins (TAYLOR, 1999). There are two isoenzymes of COX. Cyclooxygenase-1 (COX-1) is a constitutive enzyme that is responsible for maintaining a range of homeostatic mechanisms, such as the increase of blood flow to the gastrointestinal mucosa and to the kidney (REESE et al., 2000). Cyclooxygenase-2 (COX-2) is an enzyme responsible for the production of prostanoids, inflammatory mediators released in injured tissues that sensitize nociceptors (TAYLOR, 1999).

Carprofen and ketoprofen are proprionic acid derivatives. Both drugs are effective for postoperative pain relief in dogs and they seem well tolerated by dogs when used at the recommended dosage (PIBAROT et al., 1997; REESE et al., 2000). However, ketoprofen is a more potent inhibitor of COX-2 and thromboxane synthesis than carprofen, and can cause an increased inhibition of platelet aggregation and mucosal bleeding time (GRISNEAUX et al., 1999).

Carprofen is widely used as a preemptive analgesic and to relieve postoperative pain in dogs or in patients with articular degenerative disease (SLINGSBY & WATERMAN-PEARSON, 2002). Its exact mechanism of action has not been identified yet, but it is clear that the inhibition of prostaglandin synthesis had an important role in its pharmacologic effects. Carprofen blocks the release of prostaglandins in two complexes of inflammatory cells: the rat polimorphonuclear system (PMN) and the human synovial rheumatoid cell system, which indicates that it inhibits the acute (PMN system) and chronic (synovial system) phases of the inflammatory reaction (BARUTH et al., 1986).

Vedaprofen, also a proprionic acid derivative, has a low COX-2:COX-1 ratio of 0.8 (i.e., more activity against COX-2). Studies investigating vedaprofen in dogs and horses found that it is a safe and satisfactory NSAID to prevent the acute release of inflammatory mediators, while providing excellent gastrointestinal and renal tolerance in these especies (BERGMAN et al., 1996; LEES et al., 1998). Although the pharmacokinetics of vedaprofen has been studied in dogs (HOEIJMAKERS et al., 1994), little information is available on its postoperative analgesic effects.

Detection of pain in animals can be notoriously difficult because of the complexity of pain physiology and an inability of animals to verbally describe symptoms of pain; however pain assessment has been hampered by lack of a standard method of evaluation. Visual analogue scale (VAS) has been used to assess postoperative pain in dogs, as well as a numerical rating scale used to account for changes in physiologic and behavioral responses. The University of Melbourne Pain Scale has been reported to be as reliable and reproducible for pain assessment in dogs as the VAS (FIRTH & HALDANE, 1999).

Therefore, with this study we aimed to investigate the efficacy of vedaproven for alleviation of postoperative pain after ovariohysterectomy in bitches, and compare its analgesic effects with those provided by ketoprofen and carprofen, two commonly NSAIDs, widely used in small animal practice.

MATERIALS AND METHODS

Animals

Twenty-one female dogs (mean bodyweight 13.9 ± 5.1kg; mean age 2.3 ± 0.9 years) undergoing routine ovariohysterectomy in the small animal teaching hospital were recruited for this study. Physical examination, complete blood count and biochemical serum analysis were performed in all dogs. To be included in this study no concurrent medications could have been used for fifteen days before the procedure. Informed owner consent was granted for the use of the animals. Food and water was withheld from all dogs participating in this study for 12 and two hours, respectively.

The dogs were randomly assigned to one of the three groups as follows; vedaprofen[a] at 0.5mg kg^{-1} (n=7), carprofen[b] at 2.2mg kg^{-1} (n=7) or ketoprofen[c] at 2.2mg kg^{-1} (n=7). All drugs were given orally by the anesthetist two hours before the anesthetic premedication under blind conditions. Assessments were made by a researcher unaware of which treatment each dog had received.

Ovariohysterectomy was performed under general anesthesia. Dogs were premedicated with intramuscular (i.m.) acepromazine[d] 0.05mg kg^{-1}, given one hour before anaesthetic induction. Anesthesia was induced with propofol[e], 5mg kg^{-1} intravenously (i.v.). After endotracheal intubation, anesthesia was maintained using halothane[f] at a concentration of 1 to 2% delivered in oxygen by using a pressurized vaporizer, via a small animal rebreathing circuit. Anesthetic was kept constant by the use of classical signs of anesthetic depth and was adjusted if animals showed a 20% increase in heart or respiratory rate, or in systolic arterial pressure. Lactate Ringer's solution was administered i.v. during anesthesia at a rate of 10mg kg^{-1} h^{-1}. All ovariohysterectomies were performed by a single trained surgeon.

Bodyweight of dogs, duration of anesthesia, duration of surgery and time to extubation were recorded.

Pre- and postostoperative measurements

Pre-and postoperative assessments were recorded 2 hours before premedication (basal value), 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours after extubation. For each time point the dogs were subjectively assessed by visual analogue scale (VAS) by a single trained researcher (ALS) as previously described in cats (SLINGSBY & WATER-PEARSON, 2000). In this scale, a 10cm line is drawn in a paper and its beginning is marked with 0 (no signs of pain), and 10 at the end (the worst pain imaginable). The evaluator chose a point in the line which, in accordance with his clinical experience and criteria, reflected the degree of pain experienced by the animal. The cage was opened and dogs were scored for signs of pain by a second evaluator (BTL). The scoring system used to evaluate the degree of pain in dogs was the University of Melbourne Pain Scale (UMPS) which incorporates behavioral responses and physiological data. The minimum possible score obtained by the use of this scale is 0, the maximum possible score is 27 (FIRTH & HALDANE, 1999).

Blood samples

After pain measurements were recorded, a venous blood sample was collected for determination of serum cortisol and glucose levels before and 1, 4, 8, 12, 24 hours after extubation. Blood samples were obtained by means of a previously placed catheter in the jugular vein of each dog. The serum samples for cortisol levels were frozen at -20°C until all data collection was complete. Cortisol concentration was determined by the use of solid radioimmunoassay[g].

Rescue intervention analgesia

If a dog appeared uncomfortable at any point during the postoperative period, or if the total score of UMPS scale was higher than 9, butorphanol[h] was administered at 0.3mg kg^{-1} as a rescue analgesic. After the experimental study, analgesic therapy was prescribed for all the patients for at least three days with the NSAID used preemptively.

Statistical analysis

Data were examined for normal distribution using a correlation test for normality. The data were found to fit the criteria for parametric statistitics. Bodyweight of dogs, duration of anesthesia, duration of surgery and time to extubation were examined among groups using a Student's t test. The data for the UMPS scores were examined among groups at each time point by a two-way ANOVA followed by post-hoc one-way ANOVA with Bonferroni adjustment for multiple tests. VAS scores were examined by Friedman tests, to assess the effect of treatment, followed by post-hoc Kruskall-Wallis test, with Bonferroni adjustments for multiple tests. Serum cortisol and glucose levels were examined using a two sample t test using a software program[i]. Spearman's correlation was used to relate VAS scores to UMPS scores, as well as serum cortisol and glucose levels to pain scores. Within each group, the measurement of serum cortisol level, serum glucose level and pain scores were tested for difference from the basal value. Since these were paired data, Wilcoxon's signed rank test was used. Differences were considered to be significant if $P<0.05$.

RESULTS

There were no significant differences among groups for bodyweight, duration of anesthesia and duration of surgery (Table 1).
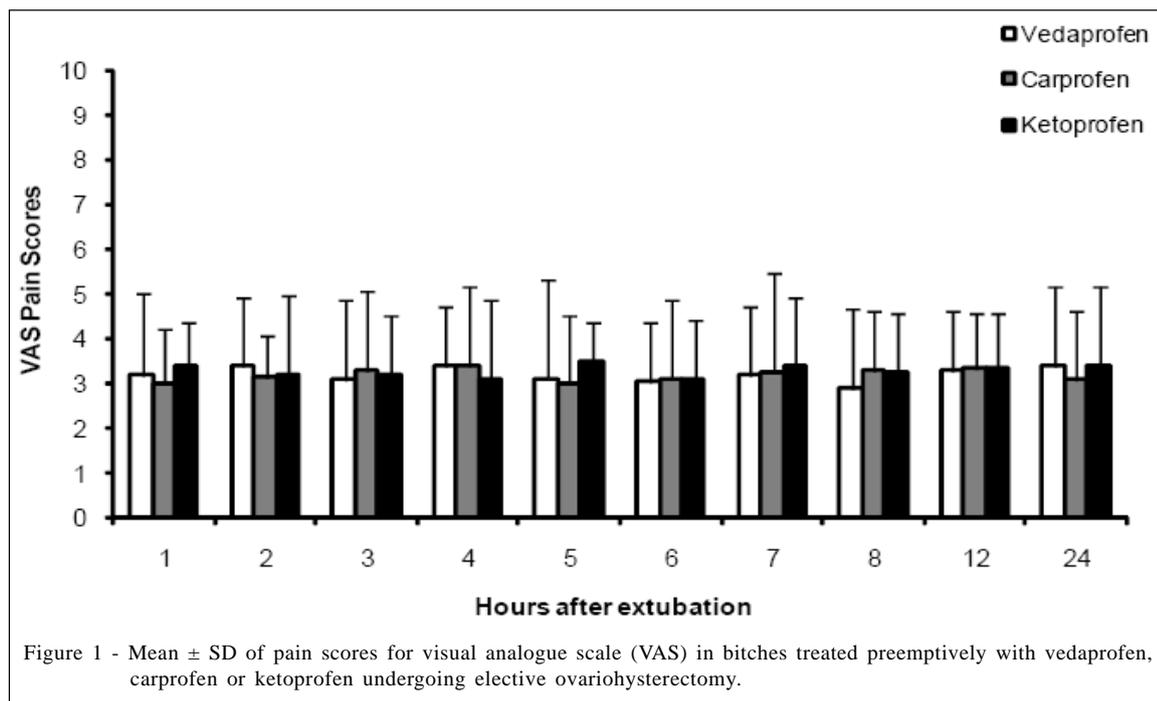
VAS scores

Basal VAS scores are not shown in figure 1 because the dogs were not in pain prior to surgery and their scores were zero. Postoperative VAS pain scores were relatively low for all groups. There were no significant differences at any time in VAS pain scores among groups. During all period of measurements, the pain scores in the vedaprofen, carprofen and ketoprofen groups were almost identical.

UMPS scores

Significant differences in UMPS scores were not also detected among groups at at any time of data collection. Postoperative UMPS scores were relatively low for all groups up to 24 hours after extubation. There was a strong correlation between the VAS pain scores and UMPS pain scores in all groups (Figure 2).

Table 1 - Mean ± SD of duration of anesthesia, duration of surgery and time to extubation in bitches treated preemptively with vedaprofen, carprofen or ketoprofen undergoing elective ovariohysterectomy.

Group	Weight (kg)	Duration of anesthesia (min)	Duration of surgery (min)	Time to extubation (min)
Vedaprofen (0.5mg kg^{-1})	16.8±7.4	35.6±2.6	28.5±3.2	5.3±5.9
Carprofen (2.2mg kg^{-1})	17.7±7.8	38.6±2.9	30.3±3.4	3.6±2.6
Ketoprofen (2.2mg kg^{-1})	17.9±6.2	37.3±4.2	30.0±2.5	4.3±6.7

Figure 1 - Mean ± SD of pain scores for visual analogue scale (VAS) in bitches treated preemptively with vedaprofen, carprofen or ketoprofen undergoing elective ovariohysterectomy.

Serum cortisol and glucose concentrations

Table 2 shows the values for pre- and postoperative plasma cortisol and glucose concentrations (mean±SD). There was a significant increase in plasma cortisol and glucose levels at one hour after extubation for all groups compared to basal values as well as to other time points. No other significant changes were observed in the groups. There was no correlation between pain scores and concurrent cortisol or glucose levels at any time period in either group.

Rescue intervention analgesia

No dog required butorphanol during the period of measurements. After the data collection, all dogs received butorphanol at 0.4mg kg^{-1}, subcutaneously.

Figure 2 - Mean ± SD of pain scores of University of Melbourne Pain Scale in bitches treated preemptively with vedaprofen, carprofen or ketoprofen undergoing elective ovariohysterectomy.
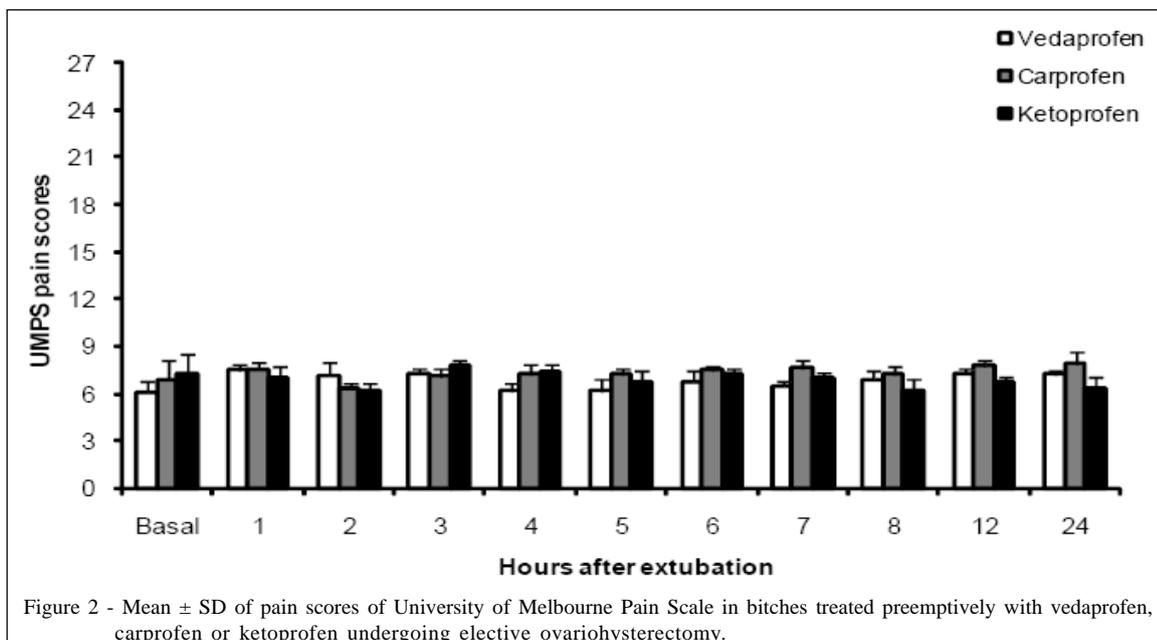
Table 2 - Mean ± SD of cortisol and glucose concentrations in bitches treated preemptively with vedaprofen, carprofen or ketoprofen undergoing elective ovariohysterectomy.

	Group	Basal	1	4	8	12	24
			---------------------------Hours after extubation---------------------------				
Cortisol concetration (ng dl^{-1})	Vedaprofen	14.5 ± 3.5	43.9 ± 12.3*	23.6 ± 7.7	16.3 ± 5.8	18.7 ± 6.2	13.9 ± 4.2
	Carprofen	13.2 ± 2.2	52.5 ± 17.9*	17.2 ± 9.6	10.3 ± 8.5	11.0 ± 9.4	14.1 ± 5.7
	Ketoprofen	18.7 ± 5.9	44.2 ± 18.2*	17.2 ± 6.1	11.2 ± 4.7	22.3 ± 12.7	10.3 ± 6.9
Glucose concentration (mg dl^{-1})	Vedaprofen	51.2 ± 10.8	90.9 ± 25.6*	86.7 ± 17.2	72.3 ± 15.7	75.0 ± 13.9	59.3 ± 14.3
	Carprofen	67.3 ± 14.6	89.3 ± 27.0*	71.2 ± 19.7	71.2 ± 12.9	72.0 ± 13.1	62.4 ± 10.7
	Ketoprofen	62.5 ± 16.9	88.8 ± 22.4*	76.1 ± 14.6	72.0 ± 10.2	72.6 ± 10.8	70.2 ± 16.5

* Value significantly different from basal value (P<0.05).

DISCUSSION

The NSAIDs were administered preoperatively before premedication because the timing of NSAIDs administration plays an important role in optimization of postoperative pain control (GRISNEAUX et al., 1999). LASCELLES et al. (1998) found a beneficial effect of preoperative carprofen administration over postoperative administration in dogs undergoing ovariohysterectomy, and probably this effect resulted from a positive pre-emptive effect of NSAIDs on peripheral and central decrease sensibilization of structures involved in hyperalgesia and allodynia (GRISNEAUX et al., 1999). The absence of dogs that required rescue interventional analgesia in our study probably supports the beneficial effect of preoperative use of NSAIDs as previously described in dogs undergoing ovariohysterectomy (LASCELLES et al., 1998).

Inhibition of COX by NSAIDs interferes with renal perfusion and dogs are particularly susceptile to developing acute renal failure in the presence of systemic hypotension (TAYLOR, 1999). Thus, arterial blood pressure and fluid therapy should be adequately monitored to maintain good cardiovascular function if any NSAID is administered pre-emptively for postoperative pain control (GRISNEAUX et al., 1999). Despite vedaprofen was well tolerated by most of the dogs with acute and chronic musculosketal pain (NELL et al., 2002), determination of bleeding time and serum urea nitrogen and creatinine concentrations before, during, and after surgery could provide additional information about the impact vedaprofen has on blood coagulation and renal function.

Postoperative analgesia by the use of the three NSAIDs (vedaprofen, carprofen and ketoprofen) has not been compared previously in dogs. Studies demonstrated that ketoprofen and carprofen are effective for relief of postoperative pain without significant differences between their analgesic efficacy in dogs (GRISNEAUX et al., 1999) and cats (SLINGBY & WATER-PEARSON, 2000).

Significant differences on pain scores and cortisol concentrations among groups were not detected during the 24 hours after surgery and, on the basis of these results, vedaprofen given prior to ovariohysterectomy provides similar levels and duration of postoperative analgesia as that of carprofen or ketoprofen in dogs. Further studies are required to determine the efficacy of vedaprofen in more painful surgical procedures (i.e., orthopedic surgeries).

VAS and numerical scales have been successfully used to evaluate pain in dogs (CONZEMIUS et al., 1997; FIRTH & HALDANE, 1999; GRISNEAUX et al., 1999) and cats (SMITH et al., 1996; SLINGSBY & WATER-PEARSON, 2000). Although the scales appear to be similarly precise and accurate, even when used to multiple observers, the VAS is reportedly more sensitive in humans (MANNE et al., 1992). However, CONZEMIUS et al. (1997) found a great correlation between VAS and a numerical rating scale in dogs undergoing orthopedic surgery. Although each scoring system was assigned by one individual, this finding supports our results that there is a strong correlation between VAS and UMPS pain scores in dogs.

As observed in our study, subjective measures of pain (i.e, pain assessment scales) and objectives variables (i.e., physilogical parameters, cortisol and glucose concentrations) are reliable indicators of pain in dogs (FIRTH & HALDANE, 1999; LASCELLES et al., 1998). Despite this, a strong correlation has not been detected between these commonly employed measures of pain in dogs and cats (SMITH et al., 1996; CONZEMIUS et al., 1997). Serum cortisol concentration is recognized as one of the most objective criteria for pain assessment in animals (SMITH et al., 1996; GRISNEAUX et al., 1999). However, determination of serum cortisol concentration is not usefull in clinical management of acute postoperative

pain, as they are not rapidly available for in-house situations. Therefore, pain scoring systems must be relied to assess the need for pain relief.

Cortisol concentration and glucose levels were significantly higher within 1 hour after extubation for all groups, and one could argue that VAS and UMPS scores does not seem to be effective for accurate detection of postoperative pain in dogs undergoing ovariohysterectomy. Similar results were also observed in clinical evaluation of postoperative pain in dogs undergoing orthopedic surgery (GRISNEAUX et al., 1999; REESE et al., 2000). In these studies, dogs given NSAIDs or placebo showed elevated serum cortisol levels only in the first hour after surgery, which probably was an indicative of excitement or stress related to the anesthetic recovery.

CONCLUSIONS

Vedaprofen provides satisfactory postoperative analgesia that appears to be equal to that of carprofen and ketoprofen in dogs undergoing ovariohysterectomy. The use of this NSAID probably represents an useful and safe alternative for preemptive protocols in the acute postoperative pain relief in small animal practice.

SOURCES AND MANUFACTURERS

[a] Quadrisol®, Intervet – Brasil
[b] Rymadil®, Pfizer – Brasil
[c] Ketoprofen®, Merial – Brasil
[d] Acepran®, Univet – Brasil
[e] Propoabbott®, Abbott- Brasil
[f] Halothano®, Cristália – Brasil
[g] Solid Immunoassay CORT-CT-2, CIS – Bio International
[h] Torbugesic®, Fort Dodge – Brasil
[i] Instat GraPhpad®, GraPhpad Software Inc. – U.S.A.

ETHICAL AND WELL-BEING COMMITTEE

The experimental protocol was approved by the ethics and animal well-being committee of the University of Franca - UNIFRAN, process nº 033/07A

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