Intra- and post-operative analgesic effects of carprofen in medetomidine premedicated dogs undergoing ovariectiony

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Intra- and post-operative analgesic effects of pre-operative administration of carprofen were investigated in 16 medetomidine-premedicated dogs undergoing elective ovariectiony. Dogs were randomly allocated into carprofen (n=8; 4 mg/kg, intramuscularly) or placebo group (n=8). After medetomidine (1000 µg/m², intramuscularly) premedication, they were induced with propofol (1 mg/kg, intravenously) and maintained with isoflurane (FECO2 1.0 %) in 100% oxygen. During anaesthesia, the analgesia was assessed in terms of changes in heart rate, respiratory rate and arterial blood pressure as a response to the surgery. Assessments of post-operative sedation (simple numerical rating scale) and pain (multifactorial pain scale) were made at 15 minutes, 30 minutes, 1, 2, 3, 4, 5, and 6 hours after the surgery. In addition, pulse rate, respiratory rate and body temperature were measured at the same time. During anaesthesia, lower heart rate, respiratory rate and mean arterial blood pressure and higher tidal volume of respiration were observed in the carprofen group. Post-operative pain score was relatively low in both groups of dogs, however it was higher, but not significantly, in the placebo group. There was no difference between the groups in terms of respiratory and pulse rate after surgery. The post-operative sedation score was higher in the placebo group only in the early post-operative period, most probably due to misinterpretation of pain behaviour. Carprofen together with other anaesthetic drugs provided sufficient intra-operative analgesia only until major painful surgical stimulus occurred, after which analgesia had to be supplemented with a subanaesthetic dose of ketamine. Comparing to that analgesia was insufficient in the placebo group throughout the procedure. The post-operative pain scoring system was probably not sensitive enough to detect the differences between the groups; however, the effects of other drugs that extended in the post-operative period may be responsible for a low post-operative pain score in both groups of dogs.

Key words: analgesia, carprofen, dogs, medetomidine, pain assessment
INTRODUCTION

For a long time opioids have been used as a single analgesic drug in veterinary practice. In recent years, there have been significant advances in the control of pain in animals (Lascelles 1996). Multimodal or balanced analgesic regimens that involve the use of combination of two or more analgesic drugs have been implemented to provide either an additive or synergistic analgesic effect of different drugs used (Dahl and Kehlet 1993). This approach is thought to be more likely to provide optimum analgesia than the use of a single analgesic agent (Kehlet 1994). Combinations of opioids and non-steroidal anti-inflammatory drugs (NSAID) are currently used in veterinary practice.

It has been realized as well, that the timing of analgesic intervention may have a significant bearing on postoperative pain. The changes in central processing of noxious signals occurring in response to peripheral injury could be markedly decreased or prevented by preinjury treatment with opioids or NSAIDs. These treatments have been far less effective if administered after the injury was initiated (Strub et al., 1982, Woolf and Wall 1986, Coderre et al., 1993). The use of analgesics before the noxious stimulus may markedly reduce the severity of postoperative pain, and pre-emptive analgesia has been quickly transposed to the clinical practice.

Carprofen, the NSAID licensed for peri- and post-operative use in dogs is a propionic acid derivative (6-chloro-alpha-methyl-carbazole-2-acetic-acid) that, at therapeutic doses, seems to be a poor inhibitor of prostaglandin synthetase i.e. cyclooxygenase, the enzyme responsible for the synthesis of inflammatory mediators produced by tissue damage (Strub et al., 1982). Despite the apparent lack of cyclooxygenase inhibition, studies have shown it to be a good analgesic in both acute and chronic pain states, and to be a very effective analgesic in dogs undergoing surgical procedures (Nolan and Reid 1993, Lascelles et al., 1994).

Medetomidine is a potent and highly specific α2-adrenergic agonist that provides reliable sedation, analgesia, muscle relaxation, and anxiolysis, as well as a decrease in the anaesthetic requirements of injectable and inhalant agents. It is frequently used as a premedication drug before general anaesthesia in dogs and cats (Sinclair 2003). Lower doses of medetomidine ranging from 2 to 10 μg/kg have been combined with various opioids such as butorphanol, oxymorphone, hydromorphone, buprenorphine and meperidine to enhance sedation and analgesia, while potentially reducing the duration and severity of the adverse cardiovascular effects associated with medetomidine use in higher doses (Pypendop and Verstegen 1998, Sinclair 2003).

To our knowledge, there have been no published studies demonstrating the efficacy of pre-operative administration of carprofen to medetomidine-premedicated dogs in the control of intra- and post-operative pain. The aim of the present study was to investigate intra- and post-operative analgesic effects of carprofen in medetomidine-premedicated dogs undergoing ovariectomy.
MATERIAL AND METHODS

Animals

Sixteen healthy bitches admitted for elective ovariectomy to the Clinic for Small Animal Medicine and Surgery, Veterinary Faculty in Ljubljana, Slovenia were entered into the study. A variety of breeds between 6.5 months and 8 years of age were represented; the dogs weighed between 9.5 and 40.5 kg. After admission to the hospital, all dogs were housed in the same surgical ward and were allowed a minimum of one hour for acclimisation to the hospital surroundings before other activities were initiated. To be included in the study, the dogs were required to have a physical examination and pre-operative blood analysis i.e. complete blood count and serum biochemistry profile including blood urea nitrogen, creatinine, potassium, sodium and chloride. No administration of medications one month before the trial was permitted. The dogs were withheld food for 12 hours and were allowed to have access to water up until two hours before induction of anaesthesia.

Study design

Eight of the dogs were given carprofen (Rimadyl, Pfizer) 4 mg/kg intramuscularly and eight were given placebo (Aqua redestillata, Pliva) 0.08 ml/kg intramuscularly into the left caudal thigh muscles. The volume of placebo was equal to the volume of carprofen used. The trial was conducted under double blind conditions. The choice of drug given to each dog was determined by the allocation of a random number. The drugs were administered by one of the investigators and the other two, who did not know which drug the dog had received, carried out all the assessments throughout the procedure.

Dogs were premedicated with medetomidine (Domitor, Orion) 1000 µg/m² of body surface intramuscularly into the right caudal thigh muscles, given about 20 minutes after carprofen or placebo administration. They were left undisturbed 20 minutes after medetomidine administration, after which the pulse rate (a. femoralis), respiratory rate and rectal body temperature were measured. A catheter was introduced into the cephalic vein and anaesthesia was induced with propofol (Diprivan, Zeneca Pharmaceuticals Ltd) 1 mg/kg intravenously. The dogs were endotracheally intubated and connected to an anaesthesia machine (Dräger Tiberius 800) using a circle circuit. Anaesthesia was maintained using isoflurane (Isofluran, Torrex Pharma GmbH) at end-tidal isoflurane concentration \( FE'ISO \) 1.0 % delivered in 100% oxygen at a flow 20 ml/kg/min. The dogs were allowed to breathe spontaneously throughout the procedure. Atipamezole (Antisedan, Orion) 2500 µg/m² of body surface was administered intramuscularly 15 minutes after the end of the surgery to antagonise the effects of medetomidine.

A catheter was introduced percutaneously into a femoral artery for the purpose of monitoring arterial blood pressure. A urinary catheter was introduced and the bladder evacuated. The dogs were positioned in a dorsal recumbency on a heated surgical table (33°C) during anaesthesia. Ovariectomy was performed through a ventral midline approach after appropriate clipping and surgical
preparation of the area. The duration of surgery was kept to between 20 and 40 minutes, and the duration of anaesthesia to approximately 70 minutes.

The following parameters were recorded during anaesthesia: heart rate (HR), mean arterial blood pressure (MAP), oesophageal body temperature (T) and ECG (Hewlett Packard 78354A), respiratory rate (RR), end-tidal CO₂ (ETCO₂), F₂ISO and arterial oxygen saturation measured by pulse oximetry (SpO₂; Ohmeda 5250 RGM), tidal volume of respiration (TV; mechanical volumetry, Dräger Tiberius 800). Measurements were taken at the following phases of surgery: baseline (1), skin incision (2), incision of abdominal wall (3), traction of left ovarian ligament (4), no surgical stimulation (5), traction of right ovarian ligament (6), suturing the abdominal wall (7), suturing the skin (8), end of the surgery (9), 15 minutes after the end of the surgery (10).

Assessments of sedation and analgesia

During general anaesthesia, the dogs were monitored for signs of nociception including the changes in HR, MAP, RR and TV as a response to the painful surgical stimulation. Subanaesthetic dose of ketamine (Ketanest, Parke-Davis, 0.5 mg/kg intravenously) was given, when additional analgesia was thought to be necessary (20% or more increase in HR, RR or MAP, or presence of spontaneous movements).

Assessments of sedation and postoperative pain/discomfort were performed 15 minutes, 30 minutes, 1, 2, 3, 4, 5 and 6 hours after the end of the surgery when the dogs were discharged. The dogs were provided with additional carprofen for 2 days (2 mg/kg/12 hours peroraly). The dogs that did not receive carprofen before the surgery were given carprofen 4 mg/kg intramuscularly by a third person for ethical reasons at the time of discharge.

Each dog was monitored continuously and attended to if distressed during the postoperative observation period. The rescue protocol with methadone (Heptanon, Pliva) 0.3 mg/kg subcutaneously was provided in a case of significant pain i.e. when the pain score was above 6 on the multifactorial pain scale.

Postoperative sedation was assessed by: observing the dog’s posture, its degree of mental alertness and its ability to stand and walk. In the discontinuous scoring system using simple numerical rating scale it was scored as follows: 0 fully alert and able to stand and walk, 1 alert and able to maintain sternal recumbency, not stable when trying to walk, 2 drowsy and able to maintain sternal recumbency but unable to stand, 3 fast asleep.

The degree of post-operative pain/discomfort was assessed with multifactor pain scale consisting of a number of simple descriptive scale values relating to the particular aspects of behaviour that may be associated with pain (Table 1). The sum of numeric scores ranged from 0 to 9 as follows: 0 complete analgesia, with no overt signs of discomfort and no reaction to firm pressure, 1 - 3 good analgesia, with no overt signs of discomfort but reaction to firm pressure, 4 - 6 moderate analgesia, with some overt signs of discomfort which were made worse by firm pressure, 7 - 9 poor or no analgesia, with obvious signs of persistent discomfort made worse by firm pressure. In addition to this scoring system, pulse rate, respiratory rate and rectal body temperature were measured at each assessment.
Table 1. Multifactorial pain scale

<table>
<thead>
<tr>
<th>Signs of crying and whimpering</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>quiet, peaceful</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>occasional vocalisation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vocalising most of the time, animal can not be calmed down with patting or gentle talking</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Movements</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>comfortable at moving, otherwise quiet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>occasionally changing the position looking for more comfortable one, but not interfering with the wound</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>changing the position most of the time, looking to the surgical wound, trying to lick it</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Restlessness and discomfort</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>peaceful, but interested in surroundings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moderately restless</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anxious, stressed</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response to the firm pressure applied adjacent to the surgical wound</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>no reaction to firm pressure in terms of vocalisation, turning the head towards the wound and trying to bite the assessor, moving away of the assessor, anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reacts to firm pressure when repeated four times</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reacts to firm pressure when repeated three times</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>reacts to firm pressure immediately or when the pressure to the wound is repeated twice</td>
<td></td>
<td></td>
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</tbody>
</table>

**Statistical analysis**

The data were analysed by use of commercial software (SPSS 10.0 for Windows). Unless otherwise stated, all reported values are given as mean ±SD. Measurements of physiological parameters such as RR, TV, T, HR, pulse rate and MAP during and after the surgery were compared by using two-way ANOVA. The sedation and pain scores were compared by the Kruskal-Wallis non-parametric test at each time point. Student’s paired t-test was used to assess the differences in the pulse rate, RR and T before and after medetomidine premedication. A value of \( P \leq 0.05 \) was considered significant.

**RESULTS**

Pulse rate significantly decreased after medetomidine administration from 115.1±14.2 to 53.2±19.4 beats/min, and respiratory rate from 98.7±34.8 to 30.7±36.5 breaths/min in the carprofen group. In the placebo group, pulse rate significantly decreased after medetomidine administration from 115.7±7.5 to 51.0±14.1 beats/min, and respiratory rate from 101.4±31.8 to 20.1±4.0 breaths/min. Body temperature slightly increased after medetomidine administration in both treatment groups i.e. from 38.7±0.5 to 38.8±0.6°C in the carprofen group and from 39.0±0.4 to 39.2±0.5°C in the placebo group.
During anaesthesia, the heart rate was higher in the placebo group. The difference was significant only at phase 4 i.e. at first major painful stimulus (traction of left ovarian ligament) when the HR increased in both treatment groups (Fig 1).

Mean arterial pressure was higher in the placebo group. The difference was significant at phases 1 to 3, after which MAP increased in both treatment groups (Fig 2).

Respiratory rate was higher in the placebo group with the only significant difference at phase 8 (suturing the skin). An increase in RR was noted in both treatment groups at the two most painful stimuli (traction of left and right ovarian ligament) (Fig 3).

Tidal volume of respiration was higher in the carprofen group except at phase 7 (suturing the abdominal wall). The difference between the treatment groups was not significant (Fig 4).

Body temperature slightly decreased during anaesthesia in both treatment groups; however the temperature was within the physiological limits throughout the experiment. In the carprofen group, the temperature decreased from 38.3±0.6°C to 38.1±0.4°C, and in the placebo group from 38.3±0.7°C to 38.2±0.7°C. The difference between the groups was not significant.

Subanaesthetic dose of ketamine was given to a total of 6 dogs in the placebo group and 6 dogs in the carprofen group. Ketamine was given most often...
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Figure 2. Mean ± SD mean arterial blood pressure (MAP; mmHg) in dogs given carprofen 4 mg/kg (■, n = 8) and placebo (○, n = 8) during (phases 1–9) and at 15 minutes after the end of the surgery (phase 10). Asterisks indicate significant difference (P ≤ 0.05) between the treated groups (legend of phases – see Figure 1). 

Figure 3. Mean ± SD respiratory rate (RR; breaths/minute) in dogs given carprofen 4 mg/kg (■, n = 8) and placebo (○, n = 8) during (phases 1–9) and at 15 minutes after the end of the surgery (phase 10). Asterisk indicates significant difference (P ≤ 0.05) between the treated groups (legend of phases – see Figure 1).

at phase 4 when the first major painful stimulus occurred (pulling the left ovarian ligament) (Table 2).
Table 2. Treatments (+) with subanaesthetic doses of ketamine (0.5 mg/kg intravenously) during ovariectomy. No ketamine was given at phases 7-10.

<table>
<thead>
<tr>
<th>Phases</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog/treatment</td>
<td>1 placebo</td>
<td>2 placebo</td>
<td>3 placebo</td>
<td>4 placebo</td>
<td>5 placebo</td>
<td>6 placebo</td>
</tr>
<tr>
<td>7 placebo</td>
<td>8 placebo</td>
<td>1 carprofen</td>
<td>2 carprofen</td>
<td>3 carprofen</td>
<td>4 carprofen</td>
<td>5 carprofen</td>
</tr>
<tr>
<td>6 carprofen</td>
<td>7 carprofen</td>
<td>8 carprofen</td>
<td>Total placebo</td>
<td>Total carprofen</td>
<td></td>
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</tr>
</tbody>
</table>

Figure 4. Mean ±SD tidal volume of respiration (TV; ml/kg) in dogs given carprofen 4 mg/kg (◆, n = 8) and placebo (●, n = 8) during (phases 1 – 9) and at 15 minutes after the end of the surgery (phase 10); (legend of phases – see Figure 1)
The sedation scores were zero before the surgery in all dogs and rose to high values immediately after the surgery. At 15 minutes after surgery, 6 dogs had a sedation score of 3, one dog had a sedation score of 2 and one had a sedation score of 1 in both treatment groups. At 30 minutes after surgery i.e. 15 minutes after atipamezole administration, only 3 dogs in the placebo group had a sedation score of 1. All the dogs from the carprofen group had a sedation score 0. No sedation was detected in any of the groups by 6 hours after the surgery. There was no significant difference in sedation scores between the groups at any time of assessment.

The post-operative pain scores were higher in the placebo group except at one hour after surgery. The highest pain scores in both treatment groups were observed 30 minutes after surgery after which they decreased and remained relatively low until the end of the observation period in both treatment groups. The difference between the groups was not significant at any time of assessment (Fig 5).

In addition to the pain scoring system, no significant difference between the treatment groups was observed in post-operative pulse and respiratory rate (Table 3).

Table 3. Mean ± SD heart rate and respiratory rate of 8 dogs treated with 4 mg/kg carprofen and 8 treated with placebo preoperatively, at intervals after ovariecotomy

<table>
<thead>
<tr>
<th>Time</th>
<th>Drug</th>
<th>Heart rate (beats/minute)</th>
<th>Respiratory rate (breaths/minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 minutes</td>
<td>Carprofen</td>
<td>78.6 (25.0)</td>
<td>21.6 (11.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>86.2 (17.1)</td>
<td>31.5 (36.2)</td>
</tr>
<tr>
<td>30 minutes</td>
<td>Carprofen</td>
<td>101.6 (29.7)</td>
<td>51.0 (26.5)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>108.4 (14.8)</td>
<td>86.5 (46.3)</td>
</tr>
<tr>
<td>1 hour</td>
<td>Carprofen</td>
<td>97.9 (20.5)</td>
<td>73.2 (39.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>93.9 (12.0)</td>
<td>90.6 (45.0)</td>
</tr>
<tr>
<td>2 hours</td>
<td>Carprofen</td>
<td>94.7 (28.4)</td>
<td>71.0 (39.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>93.2 (11.6)</td>
<td>51.9 (37.6)</td>
</tr>
<tr>
<td>3 hours</td>
<td>Carprofen</td>
<td>94.5 (15.4)</td>
<td>73.5 (42.6)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>93.2 (14.4)</td>
<td>56.5 (31.4)</td>
</tr>
<tr>
<td>4 hours</td>
<td>Carprofen</td>
<td>95.0 (20.8)</td>
<td>67.2 (41.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>99.4 (12.1)</td>
<td>46.6 (22.6)</td>
</tr>
<tr>
<td>5 hours</td>
<td>Carprofen</td>
<td>94.1 (24.7)</td>
<td>73.9 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>75.4 (33.9)</td>
<td>46.1 (16.9)</td>
</tr>
<tr>
<td>6 hours</td>
<td>Carprofen</td>
<td>100.0 (24.2)</td>
<td>71.3 (41.1)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>93.6 (11.6)</td>
<td>75.4 (31.8)</td>
</tr>
</tbody>
</table>
Body temperature increased after surgery in both treatment groups, i.e. from 38.2±0.5 to 38.4±0.3 °C in the carprofen group and from 38.3±0.7 to 38.5±0.4 °C in the placebo group. The difference between the treatment groups was not significant.

A rescue protocol with methadone was not used neither in placebo nor in carprofen treated dogs.

**DISCUSSION**

Carprofen has been shown to be effective in controlling post-operative pain in dogs and cats when given before or after the surgery (4 mg/kg, single intravenous or subcutaneous dose) (Nolan and Reid 1993, Lascelles et al., 1994, Lascelles et al., 1995, Welsh et al., 1997, Balmer et al., 1998, Lascelles et al., 1998, Slingsby and Waterman-Pearson 2001, Laredo et al., 2004). However, it is unclear whether pre-operative administration of carprofen decreases the anaesthetic requirements of injectable and volatile anaesthetics i.e. whether it has an anaesthetic sparing effect or not.

It has been suggested that pre-operative administration of carprofen reduces the amount of isoflurane, as reflected by MAC (minimal alveolar concentration), needed for anaesthesia in dogs (Ko et al., 2000). These authors assumed that the data provide a strong indication that carprofen may in fact have an effect on the MAC of isoflurane in dogs, even though the differences between carprofen and control group were not significant in their study. They suspected that the inability to detect a significant decrease in MAC was the small sample size.
used and the limitations of the tail clamp method for the determination of MAC. This method probably does not adequately mimic the pain and the inflammatory responses induced by surgery. This may also help to explain the findings of Alibhai and Clarke (1996), who reported that carprofen minimally influenced the MAC of halothane in dogs and used electrical stimulation of the noxious stimulus for determining MAC.

In the present clinical study, the authors tested the hypothesis that pre-operative administration of carprofen improves not only post-operative but also intra-operative analgesia in medetomidine-premedicated dogs. Combination of two or more analgesics with different mechanisms of action enhance analgesia and reduce the risk of adverse effects (Beaver 1984). Most of the published studies (Nolan and Reid 1993, Lascelles et al. 1994, Ko et al., 2000, Slingsby and Waterman-Pearson 2001) investigated combinations of opioids and NSAID, but none of them concentrated on combined analgesic effects of NSAID and α2-adrenergic agonist.

In the present study, dogs responded to painful intra-operative stimuli with increased heart rate, arterial blood pressure and respiratory rate, and with decreased tidal volume of respiration, which is in accordance with literature data (Hall et al., 2001). Significantly lower heart rate and mean arterial blood pressure were observed in the carprofen group only in the early intra-operative period until major painful stimuli occurred (traction and severance of ovarian ligament). Respiratory rate was lower and tidal volume of respiration higher most of the time in dogs given carprofen; however the differences were not significant. Although most of the dogs from both groups required additional analgesia at the first major painful stimulus, authors speculate that carprofen provided some intra-operative analgesia during surgery.

Carprofen has been shown to be more effective when given before rather after surgery, by both mechanical threshold testing (Lascelles et al., 1997, Lascelles et al., 1998) and behavioural measures (Lascelles et al., 1997, Welsh et al., 1997). For this reason it was administered pre-operatively in the present study. To avoid masking of carprofen post-operative effects with other anaesthetic drugs an anaesthetic protocol that provided minimal post-operative effects was selected deliberately. For ethical reasons, a rescue protocol with methadone was provided, but according to selected pain-scoring system there was no need to use it in any of the dogs. Validation of a pain assessment requires inclusion of animals, which received the anaesthetic but did not undergo any surgery, to determine the effects of anaesthesia in the absence of painful procedure (Flecknell 1994). However, to include such a group was not possible owing to the clinical nature of the trial.

There was no significant difference between the dogs treated with carprofen or placebo in the present study in terms of respiratory and pulse rate after the surgery. Previous studies have failed to observe correlation between physiological measurements such as heart and respiratory rate (Holton et al., 1998) or arterial blood pressure (Pibarot et al., 1997) and the severity of pain, which may also be the case in the present study.

Pain score was higher in the placebo group (except 1 hour after the end of the surgery) in the present study, although not significantly. Authors can only
speculate that lower pain scores in carprofen treated dogs might be due to carprofen analgesic effect. The number of animals was too low to draw any firm conclusions. On the other hand, the pain scoring system was probably not sensitive enough in assessing the actual level of pain, since it is difficult to accept that none of the dogs from the placebo group required additional post-operative analgesia according to our pain assessment score.

Pain score decreased with time in both groups. T_{max} (time to reach maximum plasma concentration) of 3 hours was reported for carprofen after subcutaneous pre-operative administration in dogs (Lascelles et al., 1998). This is in accordance with analgesic activity of carprofen observed in the present study although carprofen was given intramuscularly. On the contrary, studies in horses (Higgins and Lees 1984, Lees and Higgins 1985) and dogs (Lascelles et al., 1998) suggested that plasma drug concentrations of different NSAID's are not a useful guide for their therapeutic activity at any given time.

Low postoperative pain score in both groups of dogs could have resulted from: (a) ketamine, which was used in subanaesthetic doses in both groups to improve analgesia during surgery, and has a potential for preventing hyperalgesia some 10 – 12 hours post-administration (Slingsby and Waterman-Pearson 2000); (b) a possible pre-emptive effect of medetomidine in terms of decreasing the amount of noxious information generated at the periphery, or by blocking the entry of the noxious information into the spinal cord, thus decreasing any central changes; or (c) relatively small surgical wound of maximum 3 cm associated with minimal tissue damage.

Pain assessments made immediately after surgery may be difficult to interpret because of changes associated with recovery from anaesthesia, such as residual sedation or shivering (Matthews et al., 2001). Drug-induced sedation can mask the presence of pain by dampening the overt signs even though the pain may not be attenuated, and is therefore important to distinguish between sedation and analgesia. High sedation score before atipamezole administration in the present study was most probably due to medetomidine sedative effects, and as soon as medetomidine was antagonised, sedation score decreased in both groups of dogs. All dogs from carprofen group were fully alert and able to walk 30 minutes after the end of the surgery comparing to only 5 of 8 dogs in placebo group. The authors suspect that higher sedation score in early post-operative period in placebo group was due to the presence of pain, which was probably misinterpreted in terms of sedation, since most of medetomidine sedative and analgesic effects were already antagonised.

In conclusion, the results of the present study are conflicting regarding intra- and post-operative analgesic efficacy of carprofen in medetomidine-premedicated dogs undergoing surgical procedures. The difference in antinociception between carprofen and placebo group was observed only until the first intense painful surgical stimulus occurred. The authors suspect that carprofen provides some additional intra-operative analgesia. As there was no difference in post-operative pain score it is possible that both groups were equally pain-free or painful. Based on known analgesic efficacy of carprofen under other conditions and the evidence for problems using the multifactorial pain scoring
system, the most likely explanation is that pain scoring used in the present study was not sensitive enough. On the other hand, the lack of the difference in postoperative pain score may be also attributed to the effects of other drugs used during general anaesthesia that were extended into early post-operative period.

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ANALGETSKI EFEKTI KARPROFENA TOKOM I NAKON OVARIJEKTOMIJE KUJA UZ PREMEDIKACIJU MEDETOMIDINOM

SELIŠKAR ALENKA, ROSTAHER ANA, OSTROUŠKA MAJA I BUTINAR J

SADRŽAJ

Analgetski efekti kaprofena (4 mg/kg, im) su proučavani kod 16 kuja koje su bile podvrgnute ovarijektomiji uz premedikaciju medetomidinom (1000 μg/m², im). Nakon premedikacije, anesteziija je indukovana propofolom (1 mg/kg, iv) i održavana izofluranom (FE'ISO 1.0 %) u 100% kiseoniku. Za vreme anesteziije, analgezija je procenjivana na osnovu promena frekvence rada srca, frekvence disanja i krvnog pritiska kao odgovora na hiruršku intervenciju. Procena postoperativne sedacije i osećaja bola je vršena 15. minuta, 30. minuta, 1, 2, 3, 4, 5, i 6 časova nakon same operacije. Tokom tog perioda, mereni su puls, frekvenca disanja i telašna temperatura. Za vreme anesteziije su uočene smanjena frekvencija srčanog rada i disanja, smanjen TA i povećanje respiratornog volumena kod pasa tretiranih kaprofenom. Post-operativni bol je bio relativno slabo izražen u obe grupe pasa, ali ipak nešto veći u placebo grupi. Nakon operacije, nisu zapažene razlike u frekvenciji disanja i rada srca. Kaprofen u kombinaciji sa korišćenim anestetikima daje zadovoljavajuću analgeziju za vreme operacije sve dok se ne pojave jaki bolni stimuli kada treba dodati ketamin u subanestetičkim dozama. Analgezija nije bila zadovoljavajuća u placebo grupi. Sistem procene osećaja bola nakon operacije nije bio dovoljno precisan za tačnu diferencijaciju između grupa.