EXPERIMENTAL STUDY

Evaluation of preemptive dexketoprofen trometamol effect on blood chemistry, vital signs and postoperative pain in dogs undergoing ovariohysterectomy

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Abstract: Objective: To investigate the postoperative analgesic effects of preemptive dexketoprofen trometamol in dogs subjected to ovariohysterectomy (OHE).

Material and methods: Seventeen adult bitches of various breeds were used in this study. The dogs were randomly allocated into of two groups. Subjects in the dexketoprofen trometamol (DEX) group (n=10), received intravenous (i.v.) dexketoprofen trometamol, 1 mg/kg, 15 minutes before premedication, while those assigned to the control (C) group (n=7) were given no analgesics prior to premedication. Pain level was assessed by two researchers before the administration of anaesthesia (15 minutes before start) and 0, 1, 2, 4 and 6 hours after surgery. A modified University of Melbourne Pain Scale (UMPS) was used to evaluate pain in both groups. Results: Serum cortisol level changed from 0 to 1 h and from 0 to 1 to 4 h were compared between the groups; the increase in the C group was statistically significant. The modified UMPS was applied to both groups at baseline and postoperative 1, 2, 4 and 6 h. According to this test, the values for DEX were significantly lower than controls at 4 and 6 h (p<0.001).

Conclusion: Stable vital signs with unchanged biochemical parameters on dexketoprofen administration are a promising finding. The clinical advantage shown by the pain scale difference and the low serum cortisol levels should qualify dexketoprofen for preemptive pain management in dogs (Tab. 5, Fig. 2, Ref. 30). Text in PDF www.elis.sk.

Key words: dexketoprofen trometamol, preemptive analgesia, dog, ovariohysterectomy.

Introduction

Preemptive analgesia is the preoperative prevention of pain, administered before wound associated nociceptors are stimulated, and the subsequent maintenance of analgesia. Several studies in humans confirmed that preemptive analgesia reduces postoperative pain and the need for analgesics (1–3). Perioperative elimination of pain facilitates recovery from anesthesia and increases patient well-being (4–6). Undesirable effects of postoperative pain in surgical patients, such as loss of appetite, self-trauma, maladaptive physiological response or maladaptive behaviour, prolong time to recovery (6–8).

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) of the arylpropionic acid class with analgesic and antipyretic effects (6, 9). It has been widely used as an analgesic in dogs (6, 10, 11). It acts by inhibiting cyclooxygenase enzyme-1 (COX-1) and/or COX-2, thereby inhibiting the synthesis of prostaglandins both in inflammatory processes and in healthy tissue (6, 12). Dexketoprofen trometamol is the water soluble salt of the S-isomer of ketoprofen, which is racemic (13, 14).

Few study reports are available on the analgesic efficacy of dexketoprofen in veterinary medicine (6).

In this study, the preemptive use of dexketoprofen trometamol was evaluated in dogs undergoing OHE for its effect on vital signs, some biochemical parameters and postoperative pain.

Materials and methods

Animals

Seventeen adult bitches of various breeds were used in this study. Animals were randomly divided into two groups, seven animals in the control (C), and ten in the dexketoprofen (DEX) group. Prior approval for the study was obtained from the Afyon Kocatepe University Ethical Committee; owners were informed and signed a voluntary consent for their animals to be included in the study.

Methods

Preemptive Analgesia

DEX group received 1 mg/kg dexketoprofen trometamol (Arveles®, UFSA, Turkey) i.v. 15 min. before premedication; no
Surgical procedure
Following preparation for aseptic surgery, OHE was performed through a ventral midline approach. All OHE procedures were performed by the same practitioner to avoid bias between the groups. Procedure duration was 30±5 and 34±3 min, respectively, in the control and DEX groups.

Biochemical analysis
Blood samples were collected for biochemical analysis at baseline (0 min), and postoperative 1st, 2nd, 4th and 6th hours. Total protein, urea, ALT, AST, ALB and GGT values were determined by an autoanalysis device (Cobes C111, Roche, Germany). Serum cortisol levels at 0, 1, 4, 6 and 24 hours in venous blood samples were measured by an ELISA method.

Vital parameters
Heart rate (HR), respiratory rate (RR) and body temperature were measured preoperatively at baseline (T0), and at postoperative 0 (T1), 30 (T2), 60 (T3), 90 (T4), 240 (T5) and 360 (T6) minutes.

Pain assessment
The degree of pain was assessed 15 minutes before administration of anaesthesia and 0, 1, 2, 4 and 6 hours after surgery, by the same researchers. The modified UMPS was used for this evaluation in all dogs (Tab. 1).

Statistical analysis
Data were analyzed with the help of the SPSS for Windows, 16.0, using Student’s t-test for paired samples and ANOVA for repeated measurements. Values were described by their average (mean) ± Standard Deviation (SD). The p-value lower than 0.05 was considered to be statistically significant.

Results
The mean body weight was 16.1±7.7 kg and age 1.8±0.9 years in C, while in DEX the corresponding values were, respectively, 20.5±8.3 kg and 2±1 years. Blood chemistry results are shown in Table 2. No statistically significant difference was detected between controls and DEX group at any time point for total protein, urea, ALT, ALB or GGT. An increase in AST from baseline to 1 hour in the DEX group was, however, significant, as also was the fall in the control group at 6 hours (p<0.05 for both).

The increase in serum cortisol levels of the control group from baseline to 1 h and to 1 and 4 h was significant (p<0.05). Cortisol levels increased at 6 h in the DEX group, with a statistically significant difference compared to controls (p<0.05). Cortisol levels at 24 h decreased again at 24 h, approaching baseline values (Tab. 3, Fig. 1).

Vital sign measurements are summarized in the Table 4. Heart rate was significantly increased at 90 min. in the DEX group, while an increase in control animals at 360 min compared to DEX was also found statistically significant (p<0.05). A fall in body temperature in the DEX group at postoperative 0 min compared to
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baseline was also significant (p<0.05). Body temperatures returned to baseline values at 360 min in both groups.

Modified UMPs score evolution is shown in the Table 5 and Figure 2. They were significantly lower in the DEX group at 4 and 6 hours compared to the control group (p<0.001).

Discussion

Ovariohysterectomy is a surgical procedure widely used in analgesic studies in dogs, since it causes moderate or severe postoperative pain (6, 15).

Surgical trauma activates COX-2 and prostaglandin synthesis, respectively intervening in peripheral and central nervous system sensitization. Inhibition of COX-2 up-regulation plays a key role in the analgesic effect of preoperatively administered NSAID (16).

Ketoprofen is a racemic mixture of two enantiomers. The main enantiomer, dexketoprofen [S(+)-ketoprofen], is responsible for its analgesic effect while causing fewer adverse effects than racemic ketoprofen (6, 13, 17). In human practice, dexketoprofen is used for postoperative analgesia by the oral (18), intramuscular (19, 20) or intravenous routes (21, 22). The addition of trometamol to dexketoprofen increases the absorption rate after oral administration achieving maximum plasma concentration sooner than ketoprofen and dexketoprofen. Parenteral application is more ad-

Tab. 2. Blood Chemistry Values in the Control (n=7) and Dexketoprofen (n=10) Group Dogs (mean±SD).

<table>
<thead>
<tr>
<th>Time/Group</th>
<th>Total Protein (g/dL)</th>
<th>Albumin (g/dL)</th>
<th>Urea (mg/dL)</th>
<th>ALT (IU/L)</th>
<th>AST (IU/L)</th>
<th>GGT (IU/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Preop.)</td>
<td>Control</td>
<td>6.8±0.7</td>
<td>2.9±0.1</td>
<td>9.8±0.3</td>
<td>28.1±1.8</td>
<td>31.4±5.4^cd</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>6.1±0.2</td>
<td>3.1±0.1</td>
<td>9.6±1.2</td>
<td>22.3±2.0</td>
<td>26.1±1.8^</td>
</tr>
<tr>
<td>Postop. 1 h</td>
<td>Control</td>
<td>7.3±0.7</td>
<td>3±0.1</td>
<td>10.9±0.6</td>
<td>30.1±2.4</td>
<td>37.7±3.4^cd</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>6.5±0.3</td>
<td>3.3±0.1</td>
<td>10.8±1.2</td>
<td>23.9±2.3</td>
<td>31.2±1.8^</td>
</tr>
<tr>
<td>Postop. 2 h</td>
<td>Control</td>
<td>7.4±0.5</td>
<td>3.1±0.1</td>
<td>13±0.6</td>
<td>31.6±2</td>
<td>56.5±8.5^x</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>5.7±0.2</td>
<td>3±0.1</td>
<td>13.5±1</td>
<td>23.6±2.4</td>
<td>57.9±5.5x</td>
</tr>
<tr>
<td>Postop. 4 h</td>
<td>Control</td>
<td>7.0±0.5</td>
<td>3±0.1</td>
<td>14.6±1</td>
<td>32.7±1.7</td>
<td>59.1±7.4x</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>5.6±0.2</td>
<td>3±0.1</td>
<td>14.1±1.3</td>
<td>23.5±2.1</td>
<td>70.4±7.3b</td>
</tr>
<tr>
<td>Postop. 6 h</td>
<td>Control</td>
<td>6.8±0.5</td>
<td>2.8±0.1</td>
<td>11.5±1.3</td>
<td>31.5±2</td>
<td>46.7±6.8abcd</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
<td>5.8±0.2</td>
<td>3±0.9</td>
<td>14.9±2.2</td>
<td>24.8±2.3</td>
<td>71.3±9b</td>
</tr>
</tbody>
</table>

^x,y,z Indicate a statistical difference between or among values marked by the same letter in the same column (p<0.05).

Tab. 3. Serum Cortisol Levels in Control and Dexketoprofen Group Dogs (mean±SD).

<table>
<thead>
<tr>
<th>Time/Group</th>
<th>Cortisol (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
</tr>
<tr>
<td>1 h</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
</tr>
<tr>
<td>4 h</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
</tr>
<tr>
<td>6 h</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
</tr>
<tr>
<td>24 h</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Dexketoprofen</td>
</tr>
</tbody>
</table>

Figure 1. Serum Cortisol Levels in Control and DEX Group dogs.

Figure 2. Pain Scores in Control and DEX Group Dogs (modified University of Melbourne Pain Scale).
There is no previous reports of blood chemistry parameters in dogs given dexketoprofen. In our study, both groups were evaluated for total protein, urea, ALT, AST, ALB and GGT before surgery and 1, 2, 4 and 6 h thereafter. The AST values were shown to have increased significantly in the DEX group from baseline to 1 hour after surgery; a decrease of the same enzyme level in the control group at 6 hours was also significant. The other measurements varied in both groups while remaining within their normal ranges.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. Several metabolic alterations are known to occur as the result of pain. The most important changes are the increase in the levels of stress hormones noradrenaline, adrenaline, cortisol and ACTH (23). Serum cortisol levels were measured in this study; the control group values were significantly elevated at postoperative 1 and 4 h with respect to baseline. This result is interpreted as a reduction of postoperative pain by dexketoprofen. As cortisol levels and their variation have not previously been measured in related studies, this should be seen as a relevant finding.

Ketoprofen, an NSAII, is used postoperatively in dogs for its nonselective COX inhibition (6, 24). Luna et al (25) studied the negative effects of the chronic use of ketoprofen, etodolac, meloxicam, caprofen and flunixin. They reported that ketoprofen and etodolac increase clotting time, predisposing patients to gastrointestinal bleeding. This effect on hemostasis also creates a surgical handicap by increasing the chances of intraoperative bleeding (6, 24). Some writers reported, however, that this defect has no clinical relevance (6, 26). In human medicine, dexketoprofen is considered as an excellent analgesic (22).

In this study, vital signs and a set of biochemical parameters showed limited variation in dogs given preemptive dexketoprofen. Its relevance for clinical practice is in its being the second report in its field. In the present study, vital signs and a set of biochemical parameters showed limited variation in dogs given preemptive dexketoprofen. Its relevance for clinical practice is in its being the second report in its field.
Conclusion
Considering its ease of administration, the stability of vital signs and the absence of major changes in blood chemistry, as well as the lower serum cortisol levels and the lower pain scores in the DEX group, we conclude that dexketoprofen trometamol may be used in the preemptive management of postoperative pain in dogs.

References
15. Slingsby LS, Taylor PM, Murrell JC. A study to evaluate bupivacaine at 40 mcg kg(-1) compared to 20 mcg kg(-1) as a post-operative analgesic in the dog. Vet Anaesth Analg 2011; 38: 584–593.

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