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Studies on Renal Safety and Preventive Analgesic Efficacy of Tramadol and Parecoxib in Dogs

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Thesis in fulfilment of the degree of
Doctor of Philosophy
in Veterinary Clinical Science

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ABSTRACT


Ovariobysterectomy and castration are common surgical procedures in small animal practice that can result in clinically significant postoperative pain. One way of controlling postoperative pain is administration of a single analgesic or a combination of different classes of analgesics prior to the onset of noxious stimuli. A constraint to the perioperative use of traditional opioids and non-steroidal anti-inflammatory drugs (NSAIDs) is their undesirable side effects. In this series of experiments, the preventive (pre-emptive) analgesic efficacy of two popular human analgesics, tramadol (an ‘atypical’ opioid) and parecoxib (a NSAID with selective COX-2 inhibition) was evaluated in dogs.

Initially, the efficacy and renal safety of parecoxib, tramadol and a combination of parecoxib, tramadol and pindolol (a β-adrenoceptor blocker and 5-HT1A/1B antagonist) were screened in anaesthetised healthy dogs. These analgesics increased the dogs’ nociceptive threshold to mechanical stimuli, without causing significant alterations in the dogs’ glomerular filtration rate (GFR) estimated by plasma iohexol clearance. Subsequently, the efficacy of tramadol was compared with morphine, in dogs undergoing ovariohysterectomy or castration. The Glasgow composite measure pain scale-short form score (CMPS-SF) and changes in intra-operative electroencephalogram (EEG) responses were used to assess the efficacy of analgesics. Of the three treatment groups (preoperative morphine, 0.5 mg kg⁻¹; preoperative tramadol, 3 mg kg⁻¹; a ‘combination’ of preoperative low-dose morphine, 0.1 mg kg⁻¹, and postoperative tramadol 3 mg kg⁻¹), dogs given the ‘combination’ had significantly lower pain scores after ovariohysterectomy. In castrated dogs, preoperative tramadol (3 mg kg⁻¹) and morphine (0.5 mg kg⁻¹) were tested and no significant difference in the CMPS-SF score were observed between them. Changes in EEG variables were not specific between the treatment groups in ovariohysterectomised dogs.

Finally, the efficacy of test drugs was evaluated against acute noxious electrical stimulation in anaesthetised dogs, using EEG. Median frequency of the EEG, a reliable indicator of nociception, increased significantly in tramadol and parecoxib groups, compared to morphine, after electrical stimulation. These studies demonstrated that tramadol and
parecoxib can produce analgesia in dogs with insignificant side effects. The efficacy of tramadol appears to vary with the type of noxious stimulus. A complete prevention of noxious input by administration of analgesics pre- and post-operatively could have important clinical applications.

**Key words**: tramadol, parecoxib, morphine, dogs, analgesic efficacy, anaesthesia, renal safety
ACKNOWLEDGEMENTS

At the outset, I express my sincere thanks to my supervisors Dr. Paul Chambers and Dr. Craig Johnson for their able guidance, constant support and encouragement throughout the study period. They gave me an opportunity to work in this interesting area of preventive analgesia and provided exposure and training in various techniques related to HPLC and pain assessment. Also, I would like to specifically thank Paul for his help in anaesthesia during the trials.

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<table>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>AUC</td>
<td>area under the curve</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CGRP</td>
<td>calcitonin gene related peptide</td>
</tr>
<tr>
<td>CL1</td>
<td>clearance calculated by one-compartment model</td>
</tr>
<tr>
<td>CMPS-SF</td>
<td>composite measure pain scale-short form</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>COX</td>
<td>cyclooxygenase</td>
</tr>
<tr>
<td>Craf</td>
<td>continual rate of application of force</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>cytochrome P450 2D6</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>EEG</td>
<td>electroencephalogram</td>
</tr>
<tr>
<td>ERPF</td>
<td>effective renal plasma flow</td>
</tr>
<tr>
<td>ET CO₂</td>
<td>end-tidal CO2 tension</td>
</tr>
<tr>
<td>ET HAL</td>
<td>end-tidal halothane tension</td>
</tr>
<tr>
<td>F50</td>
<td>median frequency</td>
</tr>
<tr>
<td>FFT</td>
<td>fast fourier transformation</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-amino butyric acid</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GLMM</td>
<td>generalised linear mixed models</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>IC50</td>
<td>median inhibition concentration</td>
</tr>
<tr>
<td>ICL</td>
<td>iohexol clearance</td>
</tr>
<tr>
<td>ICP-AEC</td>
<td>inductively coupled plasma-atomic emission spectroscopy</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>LD50</td>
<td>median lethal dose</td>
</tr>
<tr>
<td>LSM</td>
<td>least square means</td>
</tr>
<tr>
<td>MAP</td>
<td>mean arterial pressure</td>
</tr>
<tr>
<td>mRNA</td>
<td>messenger ribonucleic acid</td>
</tr>
<tr>
<td>NA</td>
<td>noradrenaline</td>
</tr>
<tr>
<td>NH₄OH</td>
<td>ammonium hydroxide</td>
</tr>
<tr>
<td>NK</td>
<td>neurokinin</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-Methyl D-Aspartate</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<table>
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<th>Definition</th>
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<tr>
<td>PAG</td>
<td>periaqueductal grey</td>
</tr>
<tr>
<td>PG</td>
<td>prostaglandin</td>
</tr>
<tr>
<td>PGE2</td>
<td>prostaglandin E2</td>
</tr>
<tr>
<td>PPD</td>
<td>pressure of palpation device</td>
</tr>
<tr>
<td>PR</td>
<td>pulse rate</td>
</tr>
<tr>
<td>Ptot</td>
<td>total EEG power</td>
</tr>
<tr>
<td>RBF</td>
<td>renal blood flow</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>RVM</td>
<td>rostral ventromedial medulla</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SE</td>
<td>standard error</td>
</tr>
<tr>
<td>SEF</td>
<td>spectral edge frequency 95%</td>
</tr>
<tr>
<td>SG</td>
<td>strain gauge</td>
</tr>
<tr>
<td>SP</td>
<td>substance P</td>
</tr>
<tr>
<td>SpO2</td>
<td>oxygen saturation</td>
</tr>
<tr>
<td>SRT</td>
<td>spinoreticular tract</td>
</tr>
<tr>
<td>STT</td>
<td>spinothalamic tract</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>time to maximum plasma concentration</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
<tr>
<td>VTH</td>
<td>veterinary teaching hospital</td>
</tr>
<tr>
<td>WMWodds</td>
<td>Wilcoxon-Mann-Whitney odds</td>
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