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

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ABSTRACT

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Ovariohysterectomy 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-HT_{1A/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

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LIST OF ABBREVIATIONS

5-HT	5-hydroxytryptamine
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ANOVA	analysis of variance
ATP	adenosine triphosphate
AUC	area under the curve
BUN	blood urea nitrogen
CGRP	calcitonin gene related peptide
CL1	clearance calculated by one-compartment model
CMPS-SF	composite measure pain scale-short form
CNS	central nervous system
COX	cyclooxygenase
CRAF	continual rate of application of force
CYP2D6	cytochrome P450 2D6
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EEG	electroencephalogram
ERPF	effective renal plasma flow
E_T CO ₂	end-tidal CO ₂ tension
$E_{T\text{ HAL}}$	end-tidal halothane tension
F50	median frequency
FFT	fast fourier transformation
GABA	gamma-amino butyric acid
GFR	glomerular filtration rate
GLMM	generalised linear mixed models
HPLC	high performance liquid chromatography
IC50	median inhibition concentration
ICL	iohexol clearance
ICP-AEC	inductively coupled plasma-atomic emission spectroscopy
IV	intravenous
LD50	median lethal dose
LSM	least square means
MAP	mean arterial pressure
mRNA	messenger ribonucleic acid
NA	noradrenaline
NH ₄ OH	ammonium hydroxide
NK	neurokinin
NMDA	N-Methyl D-Aspartate
NSAID	non-steroidal anti-inflammatory drug

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PAG	periaqueductal grey
PG	prostaglandin
PGE2	prostaglandin E2
PPD	pressure of palpation device
PR	pulse rate
Ptot	total EEG power
RBF	renal blood flow
RR	respiratory rate
RVM	rostral ventromedial medulla
SC	subcutaneous
SE	standard error
SEF	spectral edge frequency 95%
SG	strain gauge
SP	substance P
SpO2	oxygen saturation
SRT	spinoreticular tract
STT	spinothalamic tract
T _{max}	time to maximum plasma concentration
UV	ultraviolet
VAS	visual analogue scale
VTH	veterinary teaching hospital
WMWodds	Wilcoxon-Mann-Whitney odds