“Pharmacology of Salicin Derivatives in Sheep”

A thesis presented in partial fulfilment
of the requirements for the degree of

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in Animal Science

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Dedicated to my husband

Chandrakant Mathurkar

Abstract

Sheep suffer from pain during various husbandry practices as well as during injury or diseases such as footrot. This pain could be potentially minimised with the use of analgesics such as non-steroidal anti-inflammatory drugs (NSAID). Unfortunately, there are very few registered NSAIDs for sheep. Thus, registered analgesics for cattle, for instance ketoprofen and meloxicam are used in sheep. Again, the high cost of analgesics and associated potential side effects such as reduced fertility, gastric irritation, gastric ulcers etc. evident in other species usually limits their use in sheep. Fear of residues in meat may stop some farmers from using analgesics. Considering these problems, this study was designed as a groundwork to explore a possible and potential use of natural, inexpensive analgesic for sheep.

Salicylic acid, a derivative of salicin, is a NSAID used effectively in humans as an analgesic since ancient times in the form of willow bark and leaves. During this research study, the pharmacokinetics of salicylic acid in sheep was analysed after administration of the sodium salt of salicylic acid (sodium salicylate/NaS) intravenously and orally at different dose rates. The analgesic efficacy of salicylic acid in sheep was also studied after administration of sodium salicylate at different dose rates by measuring mechanical and thermal nociceptive thresholds. The minimum therapeutic plasma concentration of salicylic acid for analgesia in sheep ranged from 25 to 30 μg/mL, which was achieved for about 30 minutes by a 200 mg/kg intravenous dose of NaS. During this study it was discovered that thermal nociceptive threshold testing is unable to detect any analgesia from salicylic acid and ketoprofen in sheep. However, mechanical nociceptive threshold testing efficiently detected the analgesic effects of salicylic acid and the positive control, ketoprofen.

The seasonal variation of willow salicin content (principal precursor of salicylic acid in willow) was studied over a year. The salicin in willows in New Zealand is higher during the summer months as compared to the winter months of the year, and appears greater in areas subject to drought. The analgesic efficacy of willow leaves can be assessed by feeding the willow leaves to lame sheep as they readily eat willow leaves. However, to assess the analgesia produced by willow in sheep, further research is warranted.

Keywords: Salicin, sheep, salicylic acid, analgesia, HPLC, nociceptive testing, willow.

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µg	Microgram/ micrograms
ADME	Absorption, Distribution, Metabolism, Excretion
AIC	Akaike information criterion
ANOVA	Analysis of variance
A/P	Associate professor
AUC	Area under curve/ Area under concentration-time curve
AUMC	Area under the moment curve
BC	Before Christ
BIC	Bayesian information criterion
C	Concentration of the drug in the plasma
C_0	Concentration of drug at time zero
Ca^{++}	Calcium ions
CGRP	Calcitonin gene related peptide
CINODs	COX inhibition nitric oxide donors
Cl	Clearance
C_{max}	Maximum concentration in the plasma
CMPS-SF	Glasgow composite measure pain scale short form
CNS	Central nervous system
COX	Cycloxygenase
COX-1	Cycloxygenase 1
COX-2	Cycloxygenase 2
COX-3	Cycloxygenase 3
COXIBs	COX-2 selective inhibitors
CYP450	Cytochrome P450
D	Dose
Da	Dalton
DF	Descending facilitation
DI	Descending inhibition
DLF	Dorsolateral funiculus
DNA	Deoxyribonucleic acid
DP1	PGD receptor

DRG	Dorsal root ganglia
EEG	Electroencephalography
EP	E prostanoid receptor
F	Bioavailability
FDA	The Food and Drug Administration
FP	PGF receptor
Fig	Figure
G/g	gram/grams
GABA	Gamma amino butyric acid
GCMPS	Glasgow composite measure pain scale
GI	Gastro-intestinal
G-proteins	Guanosine nucleotide-binding proteins
HPLC	High performance liquid chromatography
Hr/hr	Hour
Hrs/hrs	Hours
HVA	High voltage activated
IASP	International Association for the Study of Pain
IP	PGI receptor
I/V	Intravenous/intravenously
IVABS	Institute of Veterinary, Animal and Biomedical Sciences
K_{12}/ K_{21}/ K_{10}	Inter-compartmental constants
K_a	Absorption constant
KA	Kainate
K_{el}/K_{10}	Elimination rate constant
Kg/kg	Kilogram/kilograms
L	Litre/Litres
LATU	Large Animal Teaching Unit
LLE	Liquid-liquid extraction
LOD	(Lower) limit of detection
LOX	Lipoxygenase
LTMR	Low-threshold mechanoreceptor
LTP	Low term potentiation

LVA	Low voltage activated
M^{++}	Magnesium ions
mg	Milligram/milligrams
Min	Minute/minutes
mL	Millilitre/millilitre
MNT	Mechanical nociceptive threshold testing
MRP2	Multi-drug-resistance-associated-protein type 2
MRT	Mean residence time
MS	Mass spectrometry
N	Newton/Newtons
Na^{+}	Sodium ions
NaS	Sodium salicylate
NCA	Non-compartmental analysis
NFκB	Nuclear transcription factor
NMDA	N-methyl-D-Aspartate
NO	Nitric oxide
NRS	Numerical rating scale
NS	Nociceptive specific
NSAID	Non-steroidal anti-inflammatory drug
NTS	Nucleus tractus solitaris
PAG	Peri-aquaductal grey matter
PD	Pharmacodynamics
PG	Prostaglandin
PGD	Prostaglandin D_2
PGF	Prostaglandin F_2
PGG	Prostaglandin G_2
PGI	Prostaglandin I_2
PK	Pharmacokinetics
PKC	Protein kinase
PN	Parabrachial nucleus
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
PTFE	Polytetrafluoroethylene

R^2/r^2	Correlation coefficient
R-COH	Enolic acids
R-COOH	Carboxylic acids
RPM/rpm	Revolutions per minute
RSD	Relative standard deviation
RVM	Rostral ventromedial medulla
SA	Salicylic acid
SD	Standard deviation
SDS	Simple descriptive scale
SEP	Somatosensory evoked potentials
SMT	Spinomesecephalic
SP	Substance P
SPE	Solid phase extraction
SRT	Spinoreticular
STT	Spinothalamic
$T_{1/2}$	Half-life
T_{max}	Time at which plasma drug concentration is maximum
TNF	Tumour necrosis factor
TNT	Thermal nociceptive threshold testing
TP	Thromboxane receptor
TT	Theotepa
TTX-r	Tetrodotoxin-resistant
TXA_2	Thromboxanes
VAS	Visual analogue scale
V_d	Volume of distribution
VOCC	Voltage operated calcium channels
WDR	Wide dynamic range
A	Alpha
B	Beta
Δ	Delta

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