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# Pharmacology of Analgesic Drugs in Birds

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*Thesis in fulfilment of the degree of*
**Doctor of Philosophy**
in Animal Science

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## Abstract

Analgesics drugs are widely used to alleviate pain in mammals and birds. However, in the case of birds, there is a scarcity of information on their usage and dosing regimen. A lack of pharmacokinetic knowledge can result in under or over-dosing of drugs with subsequent loss of efficacy or side-effects. Complete understanding of a drug requires knowledge of its pharmacokinetics as well as pharmacodynamics. Considering the various voids in pharmacological research in birds and in an effort to know more about pain and welfare in birds, this study was designed to study the pharmacokinetics of morphine, butorphanol, aspirin and salicylic acid in broiler chickens. Broiler chickens were used as a model for wild and rare birds. Morphine and butorphanol were injected intravenously at 2 mg/kg, while aspirin and salicylic acid were injected intravenously at 50 mg/kg.

All the analgesic drugs were well distributed in chickens. The plasma clearance for these drugs was much higher than in mammals, resulting in shorter half-lives. All the drugs remained within the theoretical therapeutic range for 2 hours.

For analgesic efficacy testing, all the drugs except aspirin were injected in lame broiler chickens at similar dose rates as in the pharmacokinetics experiment. The results from the efficacy tests suggest that butorphanol and salicylic acid provided adequate analgesia which lasted for less than 2 hours. Morphine at 2 mg/kg intravenously induced sedation and drowsiness in chickens, which might be due to the high dose. It may have analgesic effects at lower dose rates, however this needs to be further evaluated. The approximate therapeutic range in broiler chickens for butorphanol is 50 to 80 ng/mL and for salicylic acid is 50 to 110 ng/mL. The therapeutic range for butorphanol is much higher in birds as compared to mammals while for salicylic acid it is in the mammalian range. The duration of analgesia in birds could be increased by using sustained released formulation or drug delivery systems, which warrants further research.

Plasma concentrations after butorphanol given at 4 mg/kg in an injured Northern Royal Albatross under surgical conditions were also evaluated. This is the only pharmacokinetic

study of an analgesic drug in a sea bird. The pharmacokinetics of butorphanol in this albatross differed significantly from chickens, with slower clearance and lower tissue distribution, although these were much higher than in mammals. The difference in pharmacokinetic parameters could either be due to species variation or due to the continuous fluid therapy along with butorphanol administration. This albatross was suffering from a major femur fracture, which potentially altered its normal physiology and metabolism. Chickens may be used as a model of drug research for wild and rare avian species, especially for preclinical trials. The dosing regimens can be extrapolated from chicken pharmacokinetics data, but this should be done with extreme caution as pharmacokinetics are highly variable between the species.

KEYWORDS: Morphine, butorphanol, aspirin, Salicylic acid, Broiler chickens, Albatross analgesia.

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## List of Publications

Singh PM. Johnson C. Gartrell B. Mitchinson S. Chambers P. Pharmacokinetics of butorphanol in broiler chickens. *Veterinary Record*, 168: 588, 2011

Singh PM. Johnson C. Gartrell B. Mitchinson S. Chambers P. Pharmacokinetics of morphine after intravenous administration in broiler chickens. *Journal of Veterinary Pharmacology and Therapeutics* . 33(5):515-8, 2010

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# List of abbreviations

NMDA-N-Methyl-D-Aspartate
NRPG- nucleus recticularis paragigantocellularis
NRM-nucleus raphae magnus
PAG-Periaqueductal Gray
I/T- intrathecal
S/C-subcutaneous
I/M-intramuscular
I/V- intravenous
MAP- Mitogen Activated Kinases
DAG- Diacylglycerol
PKC- Protein Kinase C
MAC-Minimum Alveolar Concentration
MEC-Minimum effective concentration
NSAIDS- Non Steroidal Antiinflammatory Drugs
COX-cyclooxygenase
TXA2 and TXB2-thromboxane
M-3-G- morphine-3-glucoronide
M-6-G- morphine-6-glucoronide
LLQ-lower limit of quantification
LOD-Limit of Detection
LC/MS- Liquid Chromatography/Mass spectrophotmeter
AUC-area under the curve
AUMC- area under the moment curve
MRT- mean resident time
$V_d$- volume of distribution
$V_c$-volume of distribution, central compartment
$V_p$-volume of distribution, peripheral compartment
$V_t$- total volume of distribution
$V_{dss}$- volume of distribution, steady state
$t_{1/2\alpha}$- Distribution half life
$t_{1/2\beta}$- Elimination half life
$t_{1/2\lambda 2}$- Terminal half life
LOD-lower of detection
DAD-diode array detector
HPLC-high performance liquid chromatography
RSD- relative standard deviation
μ-mu Opioid receptor
κ-kappa Opioid receptor
σ-sigma Opioid receptor
δ-delta Opioid receptor
β-elimination Rate constant
α-distribution Rate constant
ED-Electrochemical detector
SPE-solid phase extraction
PEG-Polyethylene glycol
MSU-Microcrystalline sodium urate

OC- Obstacle course
LTL-Latency to lie
TD-Tibial dyschondroplasia

*to my parents*
*Late Dr Inderjeet Singh*
*Late Balwinder Kaur*

# Contents

CHAPTER ONE