Application of a sedation scoring system in dogs following premedication

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To Mom, Dad and Prathmesh,

You have been my inspiration and my strength. Thank you for being a part of my life!

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Abstract

Pharmacogenetics is the study of how variations in the genome influence drug pharmacokinetics (the body's effect on the drug) and pharmacodynamics (the drug's effect on the body). The *MDR1* gene codes for a membrane-bound drug transporter protein, P-glycoprotein (P-gp) that transports drugs across the cell membrane using an energy-dependent mechanism. Anecdotal reports in the literature suggested that dogs with a mutation in the *MDR1* gene (*MDR1-1*Δ) show increased sensitivity to routinely used veterinary sedatives such as acepromazine and butorphanol, resulting in increased duration and depth of sedation. This study has 3 aims. First is to gain experience with a sedation scoring system that can be used to assess the level of sedation. The second aim is to assess the difference in sedation of dogs premedicated with dexmetomidine and acepromazine. The third aim is to investigate the effect of acepromazine (n=29) and a combination of acepromazine and butorphanol (n=12) on *MDR1* genotyped rough-coated collies.

In the study assessing the sedation of dogs premedicated with dexmadetomidine and acepromazine, 30 dogs scheduled for orchidectomy were divided into two groups; the DEX group (n=15) and the ACE group (n=15). Dogs in the DEX group received dexmedetomidine (125 μg/m^2) and morphine (0.5 mg/kg) while the dogs in the ACE group received acepromazine (0.04 mg/kg) and morphine (0.5 mg/kg). The dogs were sedation scored at 0, 10, 20 and 30 minute intervals. The dogs in the DEX group had a statistically higher sedation score at 30 minutes than the dogs in the ACE group (*p* value =0.0189). Dogs premedicated with dexmedetomidine had a higher sedation score than dog's premedicated acepromazine at 30 minutes. The heart rate, respiratory rate and mean arterial blood pressure were not different between the DEX and the ACE group at 30 minutes post administration of premedication agent.

The second study investigated the effects of acepromazine and a combination of acepromazine and butorphanol in dogs carrying the *MDR1-1*Δ mutation. Genotyping for the *MDR1-1*Δ mutation was performed in 31 rough-coated collies. Dogs were considered healthy based on clinical history, physical examination, complete blood count, serum chemistry and urinalysis. Twenty-nine of the 31 rough coated collies were deemed healthy and were enrolled in the sedation trial assessing the effects of

acepromazine on the *MDR1-1*Δ mutants. A subset of the 29 rough coated collies was enrolled in the study assessing the effects of combination of acepromazine and butorphanol. The rough coated collies were divided in 3 groups based on their genotype: homozygous mutants, heterozygous carriers and normal group. After administration of acepromazine (0.04 mg/kg, IV) or a combination of acepromazine (0.04 mg/kg) and butorphanol (0.05 mg/kg), sedation scoring was performed at 0, 30 minutes, 60 minutes, 90 minutes, 2 , 2.5 , 3 , 4 and 6 hour intervals by an observer blinded to the results of the *MDR1* genotype. Following administration of acepromazine, homozygous mutant collies (*MDR1* -/-) (n = 10) reached a greater level of sedation and remained sedated for a longer duration as compared to the heterozygous carriers (*MDR1* +/-) (n =10) and wild-type collies (*MDR1* +/+) (n = 9) (p= 0.0176). A subset of 12 dogs was sedated with a combination of acepromazine (0.04 mg/kg) and butorphanol (0.05 mg/kg). Heterozygous carriers (*MDR1* -/+) had significantly higher sedation scores than homozygous mutants (*MDR1* -/-) and normal groups (*MDR1* +/+) when sedated with the combination (p=0.0423). This unexpected result may have been due to the small number of dogs tested. The author recommends lower dosing of acepromazine and butorphanol in dogs that are homozygous mutants to the *MDR1-1*Δ mutation and recommends the constant monitoring of sedation.

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Abbrevations

ABC	ATP Binding Cassette Transporter Proteins
ACE	Acepromazine Group
ATP	Adenosine Triphosphate
AUC	Area Under Curve
AV	Atrioventricular
cAMP	Cyclic Adenosine Monophosphate
CBC	Complete Blood Count
CHO	Chinese Hamster Ovary
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CYP	Cytochrome P450 enzymes
D (1 & 2)	Dopamine Receptors
DD	Deepti Deshpande
DEX	Dexmedetomidine Group
DNA	Deoxyribonucleic acid
GABA	Gamma Amino Butyric Acid
$GABA_A$	Gamma Amino Butryric Acid A Receptors
$GABA_B$	Gamma Amino Butyric Acid B Receptors
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HR	Heart Rate
IFN-gamma	Interferon gamma
IM	Intramuscular
IV	Intravenous
M (1-5)	Muscarinic Receptors
MAP	Mean Arterial Pressure
MDR1	Multidrug Resistant-1 gene
*MDR1-1*Δ	Multidrug Resistant-1-1Δ mutation
MDR1a (-/-)	Multidrug Resistant -1a Knockout
MDR1a(+/+)	Multidrug Resistant -1a Wildtype
MUAEC	Massey University Animal Ethics Committee
MUT/MUT	MDR1-1Δ homozygous mutants
MUT/N	MDR1-1Δ heterozygous carriers
MUVTH	Massey University Veterinary Teaching Hospital
N/N	MDR1-1Δ normal
NBD	Nucleotide Binding Domain
NRS	Normal Saline
NZVP	New Zealand Veterinary Pathology
PCR	Polymerase Chain Reaction
P-gp	P-glycoprotein
R	Recalculated Sedation Score
RAI	Relative Adrenal Insufficiency
RBC	Red Blood Cells
RNA	Ribonucleic acid
RYR1	Ryanodine Receptor-1
SA	Sinoatrial
SAP	Systolic Arterial Pressure
SD	Standard Deviation
SDS	Simple Descriptive Systems
TMD	Transmembrane Domain
USA	United States of America
USDA	United States Department of Agriculture
VAS	Visual Analogue Score
VCPL	Veterinary Clinical Pharmacology Laboratory
WA	Washington State