Cover photos credits: Feline tubulopapillary mammary adenocarcinoma stained for peptidylarginine deiminase (PAD2, red; DAPI nuclear stain, blue) taken by Longying (Lynn) Dong together with Drs. Anh N. Diep and Scott A. Coonrod; late “Brindle” Chocolate Labrador Retriever from Jill King; horses and cria from Dr. Julia Felippe; cat, parrots, chicken and cow from Stephanie Specchio.
Welcome to the 2011/2012 Clinical Investigators’ Day sponsored by the Cornell University College of Veterinary Medicine. The primary goal of this forum is to provide an opportunity for residents, interns and clinical fellows to showcase ongoing investigations carried out at Cornell University College of Veterinary Medicine. It is our hope that greater insights will be gained in the breadth and depth of clinical investigations conducted at the College and will serve as a catalyst to promote greater interactions among colleagues with clinical and basic science research interests.

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CLINICAL INVESTIGATORS’ DAY

Lecture Hall I
March 19, 2012
PROGRAM

8:20-8:50 Continental Breakfast (Veterinary Education Center Atrium)

8:50-9:00 Welcome & Introductions – Dr. Rory Todhunter

9:00-9:30 Presentation – Key Note Speaker

“LOW ENERGY ANTI-FIBRILLATION PACING: LOW GAIN, NO PAIN”

Dr. Robert F. Gilmour, Jr.
Professor of Physiology
Department of Biomedical Sciences
and
Associate Dean
Research and Graduate Education

9:35-10:45 Resident Presentations – Moderator: Dr. Scott Coonrod

9:35-9:45 OUTCOME AND ADVERSE EFFECTS IN DOGS WITH APPENDICULAR
OSTEOSARCOMA TREATED WITH AMPUTATION AND CISPLATIN
David Espinosa – Medical Oncology Resident

9:47-9:57 PHASE II STUDY OF ORAL DOXETAXEL AND CYCLOSPORINE IN
CANINE EPITHELIAL CANCER
Angharad Waite – Medical Oncology Resident

9:59-10:09 MORPHOLOGIC AND IMMUNOHISTOCHEMICAL CLASSIFICATION OF
CANINE COLORECTAL TUMORS
Brian Butler – Anatomic Pathology Resident

10:11-10:21 LIVER-SPECIFIC p53 LOSS PROMOTES HIGH FAT DIET-INDUCED LIVER
DISEASE AND HEPATIC TUMORIGENESIS
Erin Daugherity – Clinical Fellow, Laboratory Animal Medicine

10:23-10:33 ABSENCE OF POINT MUTATION OF PKD1 IN CATS WITH
HEPATOFOBICYSTIC DISEASE
Andrea Johnston – Small Animal Medicine Resident

10:35-10:45 THE DNA DAMAGE CHECKPOINT PROTEIN ATM PROMOTES
HEPATOCELLULAR APOPTOSIS AND FIBROSIS IN A MOUSE MODEL
OF NON-ALCOHOLIC FATTY LIVER DISEASE
Erin Daugherity – Clinical Fellow, Laboratory Animal Medicine
10:45-11:00  Break

11:00-12:10  Resident Presentations – Moderator: Dr. Marjory Brooks

11:00-11:10  COMPARISON OF THREE IMMUNOGLOBULIN G (IgG) ASSAYS FOR DIAGNOSIS OF FAILURE OF PASSIVE TRANSFER IN NEONATAL ALPACAS  
Toby Pinn – Large Animal Medicine Resident  
Pg. 7

11:12-11:22  PROCOAGULANT ACTIVITY IN HORSES: MEASUREMENT OF PLATELET-DERIVED MICROPARTICLES AND ENDOGENOUS THROMBIN POTENTIAL  
Nora Springer – Clinical Pathology Resident  
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11:24-11:34  THERAPEUTIC SERUM CONCENTRATIONS OF TRANEXAMIC ACID AND AMINOCAPROIC ACID IN DOGS  
Kelly Blackstock – Small Animal Emergency Critical Care Resident  
Pg. 9

11:36-11:46  THE RELATIONSHIP BETWEEN SERUM ADIPOKINES AND INSULIN WITH SERUM LONG CHAIN POLYUNSATURATED FATTY ACIDS IN LABRADOR RETRIEVERS  
Renee Streeter – Nutrition Resident  
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11:48-11:58  OBESITY IN COWS IS ASSOCIATED WITH INSULIN RESISTANCE AND SERUM ADIPOKINE STATUS REGARDLESS OF OMENTAL OR SUBCUTANEOUS ADIPOKINE STATUS  
Luciano Caixeta – Clinical Fellow, Cornell Ambulatory Clinic  
Pg. 11

12:00-12:10  EFFECTS OF A SYNBIOTIC ON FECAL QUALITY, SHORT-CHAIN FATTY ACIDS CONCENTRATIONS, AND THE MICROBIOME OF HEALTHY SLED DOGS  
Jason Gagne – Nutrition Resident  
Pg. 12

12:15-1:00  Lunch & Presentations - Career Opportunities in Research beyond Resident Training

“GRADUATE TRAINING PROGRAM IN COMPARATIVE MEDICINE”  
Dr. John Parker  
Associate Professor of Virology  
Baker Institute for Animal Health

“COLLEGE OF VETERINARY MEDICINE: CORNELL CLINICAL FELLOWS PROGRAM”  
Dr. Lisa Fortier  
Associate Professor  
Department of Clinical Sciences

1:05-2:15  Resident Presentations – Moderator: Dr. John Parker

1:05-1:15  GUPPIES IN THE LAB: BE CAREFUL WHAT YOU ASK FOR  
Kate Breyer – Laboratory Animal Medicine Resident  
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1:17-1:27  MODULATION OF INNATE IMMUNITY BY A BACTERIAL PHOSPHOLIPASE  
Bryant Blank – Laboratory Animal Medicine Resident  
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Key Note Speaker

Robert Gilmour, PhD, Professor of Physiology, Department of Biomedical Sciences, and Associate Dean for Research and Graduate Education. He is a member of the Graduate Fields of Molecular and Integrative Physiology, Pharmacology, Bioengineering and Computational Biology and is the Principal Investigator of two NIH training grants. His research interests are centered on theoretical and experimental studies of heart rhythm disorders. The theoretical studies use computer models and nonlinear dynamical systems theory to establish fundamental mechanisms for normal and abnormal electrical wave propagation in cardiac tissue. The experimental studies use nanofabricated multielectrode arrays and optical mapping to assess wave behavior in intact tissue preparations and nanobiohybrid gene delivery and patch clamp studies in isolated myocytes to identify the ionic bases for aberrant wave behavior. Professor Gilmour received his A.B. in English and Biology from Bowdoin College in 1973 and his Ph.D. in Pharmacology from SUNY Upstate Medical Center in 1977.

Speakers

Lisa Fortier, DVM, PhD. Board Certified Orthopedic Surgeon, Associate Professor, Department of Clinical Sciences. Dr. Fortier received her DVM from Colorado State University in 1991 and completed her Residency and Ph.D. at Cornell University between 1996-2001. She was the recipient of a Mentored Clinical Scientist Development Award from the National Institute on Aging in 2000 and has received continuous grant support from federal, state, nonprofit, and corporate entities as a faculty member of the College. Her research interests encompass cartilage biology and the development of arthritis, with the ultimate goal of identifying novel molecular targets for the treatment or prevention of arthritis. She has served on a number of committees, both nationally and locally, including serving as the first Veterinarian and woman President of the International Cartilage Repair Society, as Vice-President of the International Veterinary Regenerative Medicine Society, as a founding member of the International Equine Stem Cell Coalition. Dr. Fortier also serves on several executive advisory boards to key journals such as Veterinary Surgery, Equine Veterinary Journal, Cartilage, and American Journal of Sports Medicine. Dr. Fortier remains an active orthopedic equine surgeon and a mentor to trainees at all levels, including undergraduate students, veterinary and graduate students, and postdoctoral fellows.
John S. Parker, BVMS, Ph.D., Associate Professor of Virology. Dr. Parker received his veterinary degree from Glasgow University, Scotland, in 1983, and practiced clinical veterinary medicine for 11 years prior to pursuing a Ph.D. at Cornell University. He continued his postdoctoral training at Cornell and at the Harvard Medical School before returning to Cornell as faculty member of the Baker Institute for Animal Health. In 2005, Dr. Parker received the prestigious Burroughs Wellcome Fund award for “Investigators in Pathogenesis of Infectious Disease” and has had continuous grant support from sponsors such as the Cornell Feline Health Center, Morris Animal Foundation, NIH, and US-Israel Binational Agricultural Research Development Fund. Dr. Parker is an active teacher and strong mentor to veterinary students and veterinarians seeking advanced degree training. He is the Director of the Cornell University Leadership Program for Veterinary Students and Director of the Graduate Training Program in Comparative Medicine, both supported by the NIH and other sponsors.

Moderators

Marjory Brooks, DVM, Board Certified in Veterinary Internal Medicine, Section Director-Comparative Coagulation Laboratory, Animal Health Diagnostic Center. Dr. Brooks received her DVM in 1981 from Cornell University and received her Board Certification in Veterinary Internal Medicine in 1988. She completed her three-year intern and resident training at the Animal Medical Center in New York. Prior to her appointment at Cornell University in 1994, she was a Research Scientist at the Comparative Hematology Laboratory Wadsworth Center for Laboratories & Research at the New York State Department of Health. Dr. Brooks’ research interests are in comparative hemostasis, focusing on canine hereditary bleeding disorders, biomarkers of hypercoagulability in animals, and the mechanisms of transmembrane lipid movement in platelet activation and apoptosis.

Scott Coonrod, Ph.D., Associate Professor, Baker Institute for Animal Health. Dr. Coonrod received his undergraduate and graduate degrees from Texas A&M University, receiving his Ph.D. in Animal Science: Veterinary Physiology. He subsequently pursued post-doctoral training at the University of Virginia, where he later taught as an Assistant Professor of Research. In 2003, he joined the Department of Genetic Medicine at the Weill Cornell Medical College and in 2007 he was recruited to Cornell's Ithaca campus as an Associate Professor in the Baker Institute of Animal Health. Since the beginning of his education, Dr. Coonrod’s long term research interest and passion have focused on oocyte maturation and early development. In more recent years, he has an active program in understanding the epigenetic mechanisms underlying the ontogeny of breast cancer. His work and laboratory have been supported by the Department of Defense Era of Hope, Susan G. Komen for the Cure Foundation, and NIH.
Kirk Maurer, DVM, Ph.D., DACLAM, Cornell Center for Animal Resources Clinical Veterinarian, and Adjunct Assistant Professor, Department of Biomedical Sciences. Dr. Maurer joined the Cornell University CARE in 2008 and has been an active member of the College of Veterinary Medicine’s community since his arrival. His research focuses on characterizing the role of the immune system in cholesterol gallstone formation which is supported by the National Institutes of Health’s Mentored Clinical Scientists Development Award. He has formed numerous collaborations during his tenure here at the College and University and is also an active member of the Clinical Investigators’ Day Committee. Dr. Maurer, along with Dr. Mary Martin, Interim Attending Veterinarian, serves as co-directors of the “Cornell CARE Residency Program in Laboratory Animal Medicine” supported by the NIH and University.

John S. Parker, BVMS, Ph.D., Associate Professor of Virology. Dr. Parker received his veterinary degree from Glasgow University, Scotland, in 1983, and practiced clinical veterinary medicine for 11 years prior to pursuing a Ph.D. at Cornell University. He continued his postdoctoral training at Cornell and at the Harvard Medical School before returning to Cornell as faculty member of the Baker Institute for Animal Health. In 2005, Dr. Parker received the prestigious Burroughs Wellcome Fund award for “Investigators in Pathogenesis of Infectious Disease” and has had continuous grant support from sponsors such as the Cornell Feline Health Center, Morris Animal Foundation, NIH, and US-Israel Binational Agricultural Research Development Fund. Dr. Parker is an active teacher and strong mentor to veterinary students and veterinarians seeking advanced degree training. He is the Director of the Cornell University Leadership Program for Veterinary Students and Director of the Graduate Training Program in Comparative Medicine, both supported by the NIH and other sponsors.

Judges

Douglas Antczak, VMD, PhD, Dorothy Havemeyer McConville Professor of Equine Medicine, Baker Institute for Animal Health. After receiving his VMD at the University of Pennsylvania in 1973, Professor Antczak conducted post-graduate research in England as a Thouron Scholar, subsequently receiving his Ph.D. from Cambridge University in 1978. He has been a member of the College faculty since 1979 and served as the Director of the Baker Institute for Animal Health from 1994-2009. The Antczak Laboratory focusses on three important areas of equine medicine: immunology, reproduction, and genetics. His research has been supported by numerous granting agencies, including the Harry M. Zweig Memorial Fund for Equine Research, the Morris Animal Foundation, and the NIH. Dr. Antczak has mentored over 20 graduate students and post-doctoral fellows and has also led a long standing, summer educational program that has provided educational experiences in academic equine medicine for more than 50 veterinary students.
Brian Collins, DVM, Cornell Class of ’94, Lecturer. Joining the Cornell University Hospital for Animals just this past year, Dr. Collins is actively developing a surgery service within the Hospital’s Community Practice Service that will focus on mentoring students on hospital procedures, supervise students performing surgeries with local and regional shelters and Ithaca’s Shelter Outreach Services, and help manage the Community Practice Service operation. Prior to his faculty appointment at Cornell, he served 17 years in private practice providing him with a strong foundation in primary care medicine and surgery. He is an active member of the Ithaca community, serving as the president of the board for Ithaca’s Shelter Outreach Services, volunteering and supporting the Tompkins County SPCA, and sharing his knowledge and commitment in supporting shelter animal medicine.

Hollis Erb, DVM, Ph.D., Professor of Epidemiology, Department of Population Medicine and Diagnostic Sciences. Dr. Erb received her DVM in 1974 from the University of California-Davis and subsequently completed an Internship in Large Animal Medicine at the Ontario Veterinary College in Ontario, Canada. After receiving her Ph.D. in 1979 from the University of Guelph, Ontario, Dr. Erb joined the faculty at the College of Veterinary Medicine, Cornell University. Dr. Erb is one of the foremost academic epidemiologist in the country; she was the named recipient of the prestigious Calvin W. Schwabe award in 2009 recognizing her commitment and contributions to veterinary epidemiology and preventive medicine. She is widely known in the College of Veterinary Medicine for mentoring residents and graduate students in study design and analysis and for collaborating with College and University faculty on clinical research investigations in various animal species.

James Fox, DVM, Professor and Director of the Division of Comparative Medicine, and a Professor in the Department of Biological Engineering at the Massachusetts Institute of Technology. Dr. Fox is a Diplomate and a past president of the American College of Laboratory Animal Medicine. He has served on numerous veterinary medical boards and organizations, including AAAS, AALAS, AVMA, AAVMC, IDSA, ACLAM and ASM. His commitment and dedication to the veterinary profession are fully recognized - he has received countless scientific awards, including the AVMA’s Charles River Prize in Comparative Medicine, the AALAS Nathan Brewer Scientific Achievement Award, and the AVMA/ASLAP Excellence in Research Award. Additionally, Dr. Fox was elected to the Institute Medicine of the National Academy of Sciences in 2004. His past and current research has been funded by NIH and NCI, as well as by private industrial sources, for the past 35 years. He has been the principal investigator of an NIH postdoctoral training grant for veterinarians for the past 20 years and has trained 50 veterinarians for careers in biomedical research. He also has a NIH training for veterinary students and has introduced over 100 veterinary students to careers in biomedical research. Professor Fox is the author of over 490 articles, 80 chapters, 4 patents, and has edited and authored 13 texts, in the field of in vivo model development and comparative medicine.
David Smith, DVM, serves as New York’s State Veterinarian. He earned his DVM degree at Colorado State University in 1988. He worked for 20 years in USDA animal health, animal welfare, and food safety programs before joining the New York State Department of Agriculture and Markets in 2007 as Assistant State Veterinarian. Dr. Smith directs the Division of Animal Industry, which has broad responsibilities for agricultural animal health and pre-harvest food safety within New York State.

Bud C. Tennant, DVM, DACVIM is the James Law Professor of Comparative Medicine in the Department of Clinical Sciences. Dr. Tennant received his veterinary degree from the University of California-Davis where he also completed a clinical internship. During service in the Army Veterinary Corps, he was assigned to the Walter Reed Army Institute of Research where he served as manager of the Germfree Research Laboratory. He received post-doctoral research training as a Research Fellow in Medicine in the Gastrointestinal Unit of the Massachusetts General Hospital and served as a member of the faculty of the School of Veterinary Medicine at UC-Davis prior to joining the Cornell faculty in 1972 as Professor and Chief of Medicine. Dr. Tennant has conducted clinical and experimental research dealing primarily with the hepatic and gastrointestinal diseases of animals. He has had a significant role in development of the Eastern woodchuck (*Marmota monax*) as an animal model for studies of the pathogenesis of human hepatitis B virus (HBV) infection, of the role of this virus in hepatocarcinogenesis, and in the use of the woodchuck model in the preclinical development of drugs for treatment of HBV infection and prevention of hepatocellular carcinoma.

Terri Wheeler, MA, DVM, Pfizer Animal Health. Dr. Terri Wheeler received her DVM in 1990 from Oklahoma State University. After graduation she worked for four years at the Wright Veterinary Medical Center, a 10 doctor small animal practice in Bethlehem, Pennsylvania. After leaving practice, she went to work for Merck AgVet as a technical services veterinarian. She then spent four years as the head of microbiology and staff veterinarian at the Tufts Veterinary Diagnostic Lab in Grafton, Massachusetts. In 2000 IDEXX purchased the Diagnostic Lab and she became the head of microbiology for IDEXX laboratories for the next four years. She worked for a short time for the Rapid Assay Division (SNAP) of IDEXX before joining Pfizer in November of 2005. After five years as the Pfizer New England Area Veterinarian, she joined the Specialty Hospital Liaison group in January 2011. She currently serves on the Mass VMA Public Health Committee. Her interests include the pathophysiology and epidemiology of infectious diseases and the prevention and treatment of these diseases. In her spare time she enjoys gardening, come by and see her collection of dwarf evergreens, travel, and rooting for the Red Sox!
OUTCOME AND ADVERSE EFFECTS IN DOGS WITH APPENDICULAR OSTEOSARCOMA TREATED WITH AMPUTATION AND CISPLATIN

David R. Espinosa\textsuperscript{1}, Joseph Wakshlag\textsuperscript{1}, Cheryl Balkman\textsuperscript{1}, Kelly Hume\textsuperscript{1}
\textsuperscript{1}. College of Veterinary Medicine, Cornell University, Ithaca, NY

Project Mentor: Kelly Hume, Cheryl Balkman

\textbf{Introduction:} Osteosarcoma is the most common primary malignancy of bone in the dog. Standard treatment involves amputation or limb-sparing surgery followed by adjuvant chemotherapy. Despite this therapy, over 80\% of dogs will develop metastasis. Median survival time in dogs undergoing amputation alone ranges from 134 to 175 days. Median survival times in dogs treated with adjuvant cisplatin ranges from 262 to 413 days with dosages ranging from 40 – 70 mg/m\textsuperscript{2}. The objective of this study was to evaluate the use of adjuvant cisplatin at a dosage of 70 mg/m\textsuperscript{2} in a recent cohort of patients.

\textbf{Methods:} Medical records of dogs with appendicular osteosarcoma that underwent amputation followed by cisplatin chemotherapy at the Cornell University Oncology Service from 2000 – 2011 were retrospectively reviewed. Data collected from the medical records included: signalment, pre-treatment bloodwork, dosage of cisplatin, adverse effects, additional chemotherapy treatment, and outcome.

\textbf{Results:} 19 dogs met the criteria. The initial dosage for all patients was 70 mg/m\textsuperscript{2} of cisplatin with concurrent fluid diuresis and antiemetics. At least 1 dose of cisplatin was administered to each patient after amputation. 12/19 (63\%) dogs had cisplatin prematurely discontinued due to adverse effects. Median survival time for 16 dogs was 311 days (range, 81-663), with one dog still alive and two dogs lost to follow-up at 82 and 540 days after surgery.

\textbf{Discussion:} Despite the uniform dosing of cisplatin, median survival time was similar to that previously reported. Additional studies to evaluate prognostic factors are underway.
PHASE II STUDY OF ORAL DOCETAXEL AND CYCLOSPORINE IN CANINE EPITHELIAL CANCER

A Waite\textsuperscript{1}, C Balkman\textsuperscript{1}, D Bailey\textsuperscript{2}, M Kiselow\textsuperscript{3}, A Flory\textsuperscript{4}, Lionel D. Lewis\textsuperscript{5}, M McEntee\textsuperscript{1}

\textsuperscript{1} Cornell University Hospital for Animals, College of Veterinary Medicine, Ithaca, NY
\textsuperscript{2} Oradell Animal Hospital, Paramus, NJ
\textsuperscript{3} Sage Center for Veterinary Specialty and Emergency Care, Campbell, CA
\textsuperscript{4} Veterinary Specialty Hospital of San Diego, San Diego, CA
\textsuperscript{5} Section of Clinical Pharmacology, Department of Medicine, Dartmouth Medical School and Dartmouth Hitchcock Medical Center, Lebanon, NH.

Project Mentor: Margaret McEntee, Cheryl Balkman

Introduction: Docetaxel is a member of the taxane family of chemotherapy drugs, and is used extensively in the treatment of a range of epithelial neoplasia in humans. The goal of the current study was to determine the efficacy of oral docetaxel in combination with cyclosporine in the treatment of canine epithelial cancer.

Materials & Methods: Requirements for eligibility were histological confirmation of epithelial neoplasia, measurable disease, no chemotherapy treatment within two weeks, and ≥ three month life expectancy.

Results: Fifty-one dogs were enrolled. Two treatments were planned at two-week intervals. Monitoring consisted of weekly evaluations, with a CBC on day 7 and CBC/panel on day 14 post treatment. The most common tumor types were carcinoma, squamous cell carcinoma (SCC), and transitional cell carcinoma (TCC). Ten dogs had progressive disease at two weeks, one dog died, and one dog was withdrawn from the study. Thirty-nine dogs were given a second dose of DT/CsA with three each receiving a third or fourth dose of docetaxel. Eight dogs had a dose reduction (1.5 mg/kg). Six dogs had treatment delays.

Conclusion & Clinical Relevance: The overall response rate was 16.7% (8/48 evaluable dogs had a partial response) with 24 stable disease and 16 progressive disease. The highest response rate was seen in dogs with oral SCC (50%) with six out of 12 dogs having a partial response. As our veterinary population with oral SCC often presents with advanced disease, docetaxel serves as a significant advancement for this tumor type.
MORPHOLOGIC AND IMMUNOHISTOCHEMICAL CLASSIFICATION OF CANINE COLORECTAL TUMORS

BP Butler¹, GE Duhamel¹
¹. College of Veterinary Medicine, Cornell University, Ithaca, NY.

Project Mentor: Gerald Duhamel

Colorectal cancer (CRC) is an important disease of animals and humans. It is the third most common form of human cancer and the second leading cause of cancer-related deaths in developed Western countries. Canine CRC shares many features of this human disease. Importantly, dogs are one of few species that develop a spectrum of colorectal neoplasia similar to the progression of tumors observed in humans. The expression patterns of cell adhesion molecules in canine colorectal tumors are poorly understood. Altered Wnt signaling and impaired intercellular adhesion due to E-cadherin and β-catenin dysfunction have been implicated in many cancers, but have not been fully explored in canine colorectal tumors. The aim of this study is to analyze β-catenin cellular location and E-cadherin expression levels within the spectrum of canine colorectal tumors using immunohistochemical techniques in correlation with morphological changes.

Methods: Fifteen hyperplastic polyps, 15 adenomas, and 15 adenocarcinomas were selected from the Cornell University archives for assessment of the cadherin-catenin complex expression in parallel with markers of proliferation and tumor suppressor mutation; Ki67 and p53, respectively. Expression patterns are analyzed in conjunction with objective morphologic features of neoplastic progression to provide a basis for determining the most significant histologic predictors of malignancy.

Results: Our results to date suggest that certain morphologic features, such as: loss of goblet cell differentiation, crypt branching, nuclear stratification, and nuclear atypia, are reliable markers of oncogenesis. Objective morphologic data will be analyzed with pending immunohistochemical expression patterns of cadherin-catenin complex, Ki67, and p53.
LIVER-SPECIFIC p53 LOSS PROMOTES HIGH FAT DIET-INDUCED LIVER DISEASE AND HEPATIC TUMORIGENESIS

Erin K. Daugherity1, Robert S. Weiss1, Kirk J. Maurer1
1 College of Veterinary Medicine, Cornell University, Ithaca, NY

Project Mentor: Robert Weiss, Kirk Maurer

Introduction: Non-alcoholic fatty liver disease (NAFLD) may lead to liver failure and hepatocellular carcinoma (HCC). p53 is a tumor suppressor that also modulates hepatic cholesterol metabolism. The aim of this study was to examine the effect of liver specific loss of p53 on NAFLD severity and progression.

Methods: We compared conditional knockout (CKO) mice with liver specific p53 loss to wild-type (wt) control mice. Beginning at weaning, mice were fed either a high fat diet (HFD) or a standard diet (SD). At the conclusion of the study or when signs of liver failure ensued, mice were euthanized and samples were collected.

Results: All mice fed HFD displayed fatty liver disease. HFD fed CKO animals had significantly higher (p<0.04) mortality rates with a median survival of 24-weeks and a hazard ratio of 3.7 compared to no mortality in HFD fed wt mice for the entire study. Consistent with liver failure, HFD fed CKO mice demonstrated significantly elevated serum bilirubin (9.7±1.7 mg/dL, p=0.019) when compared to wild-type counterparts (1.2±0.9 mg/dL). Serum cholesterol levels in HFD fed CKO mice were also significantly higher (2207±264 mg/dL, p=0.0175) than wild-type counterparts (436.3 118 mg/dL). Notably, 4 CKO mice developed hepatic tumors following 30 weeks of HFD feeding, whereas no tumors developed in wild-type mice.

Conclusion: Mice with liver specific p53 loss are more susceptible to HFD-induced liver failure and hepatic tumorigenesis than wild-type mice. Furthermore, these data establish that p53 has essential functions in the liver as both a tumor suppressor and a metabolic regulator.
Andrea N. Johnston, DVM

anj8@cornell.edu

Institution and location (Chronological)      Degree       Year
Tufts University, North Grafton, MA          DVM          2005
Tufts University, North Grafton, MA          Fellowship (1) 2009-2011

Current Position: Resident, Internal Medicine – 3rd year

(1) Small Animal Medicine

ABSENCE OF POINT MUTATION OF PKD1 IN CATS WITH HEPATOFIBROCYSTIC DISEASE

AN Johnston¹, SA Center¹, J Wakshlag¹
¹. College of Veterinary Medicine, Cornell University, Ithaca, NY.

Project Mentors: Sharon Center and Joseph Wakshlag

Introduction: Autosomal dominant polycystic kidney disease (ADPKD), the most common inherited disease in cats, is also a common inherited disorder in humans. Initially described in cats of Persian ancestry, it also occurs in cats of other lineages. A causal point mutation in Polycystin 1 (PKD1) is diagnostic. Feline ADPKD varies in phenotypic expression but usually is evident by 6 months using ultrasonographic renal imaging (cystic lesions). While renal ADPKD manifestations are well documented, a subset of cats from the initial ADPKD colony concurrently demonstrated biliary fibrosis and hyperplasia consistent with a fibrocytic biliary malformation. Rare single biliary cysts were also described (lined by flattened or dysplastic biliary epithelium). To our knowledge, fibrocytic biliary disease consistent with a ductal plate malformation in the absence of polycystic renal lesions has been defined in humans, but has not been definitively associated with the feline PKD1 mutation. We hypothesize that additional fibropolycystic genetic variants exist in cats.

Materials and Methods: Using DNA extracted from paraffin embedded tissue (n=25 histopathologically confirmed hepatic fibropolycystic phenotype; n=10 PKD1 positive controls; n=5 PKD1 negative controls) we investigated whether the point mutation causal to feline ADPKD (PKD1 exon-29) exists in cats with fibropolycystic hepatic malformations lacking cystic renal lesions. A feline validated restriction fragment length polymorphism test for the PKD1 was used to detect heterozygotes.

Results: Findings confirm that some cats with fibropolycystic liver lesions lack the PKD1 point mutation.

Discussion: Accurate gene-based classification will lead to targeted therapy.
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Institution and location (Chronological) | Degree | Year
--- | --- | ---
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(1) Laboratory Animal Medicine

THE DNA DAMAGE CHECKPOINT PROTEIN ATM PROMOTES HEPATOCYTOPLASMIC APOPTOSIS AND FIBROSIS IN A MOUSE MODEL OF NON-ALCOHOLIC FATTY LIVER DISEASE

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Introduction: Steatoapoptosis is a hallmark of non-alcoholic fatty liver disease (NAFLD). We hypothesized that increased hepatocellular reactive oxygen species resulting from a high fat diet (HFD) contributes to NAFLD by promoting DNA damage and apoptosis. The DNA damage response involves the checkpoint kinase ATM, and Atm⁻/⁻ mice are susceptible to oxidative stress. We therefore used a diet induced model in Atm⁻/⁻ mice to determine the effects of Atm deficiency on steatoapoptosis and hepatic fibrosis, during NAFLD progression.

Methods: Atm⁻/⁻ and Atm⁺ (Atm⁺⁺ and Atm⁺⁻) mice were fed a high fat diet or standard diet (SD) for 8 weeks. Histological sections were scored for hepatic lipid accumulation, inflammation and fibrosis. TUNEL was utilized to quantify apoptosis, and hepatic expression of pro-apoptotic genes were quantified by qPCR. Hepatic H₂O₂ and superoxide levels, and 8-hydroxyguanosine (8-OHG) positive hepatocytes, were quantified.

Results: In both Atm-deficient and control mice, HFD feeding resulted in increased hepatic H₂O₂ and superoxide production, and caused increased hepatic steatosis, hepatitis, and DNA damage as exemplified by an increase in the percentage of 8-OHG positive hepatocytes. However, the prevalence of apoptosis (p=0.02) and the expression of the pro-apoptotic factor PUMA (p< 0.05) were significantly reduced in HFD fed Atm⁻/⁻ mice when compared to wild-type controls. HFD fed Atm⁻/⁻ mice had significantly less hepatic fibrosis than HFD fed Atm⁺ mice (p<0.05).

Conclusion: These data demonstrate that the ATM pathway responds to hepatic fat accumulation and link ATM to fatty liver-induced steatoapoptosis and fibrosis, key features of NAFLD progression.
COMPARISON OF THREE IMMUNOGLOBULIN G (IgG) ASSAYS FOR DIAGNOSIS OF FAILURE OF PASSIVE TRANSFER IN NEONATAL ALPACAS

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Project Mentor: Tracy Stokol

Measurement of serum IgG is used for assessment of passive transfer of immunity in neonatal crias. The purpose of this study was to determine whether three commercially available assays yielded comparable results for IgG in crias. Serum samples from 91 crias submitted to Clinical Pathology for routine IgG measurement were used. Samples were stored frozen until batch analysis on the same day with the three assays. IgG was measured by radial immunodiffusion (assay A) and 2 immunoturbidimetric methods - one is configured for automated chemistry analyzers (assay B) and the other is a farm-side test (assay C). Median IgG concentrations were significantly different between the three assays. Assays A and B, which used the same standard, yielded higher IgG values than assay C, resulting in a lack of concordance in 7-18% of samples at 1000 mg/dL IgG. Protein electrophoresis revealed that assay A and B standards contained mostly albumin (>60%), whereas assay C standard consisted of beta and gamma globulins. Median results from assay B after calibration with the assay C standard were not significantly different from those of assay C and diagnostic concordance between these 2 assays improved. Our results indicate that camelid IgG results are highly dependent on the assay standard and are not directly comparable between assays, potentially resulting in under-diagnosis of FPT in some crias.
PROCOAGULANT ACTIVITY IN HORSES: MEASUREMENT OF PLATELET-DERIVED MICROPARTICLES AND ENDOGENOUS THROMBIN POTENTIAL

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Project Mentor: Tracy Stokol

Co-Mentors: James L. Catalfamo, Marjory B. Brooks

Background: Thrombosis is a common sequela of systemic inflammatory disease in horses. Identification of at-risk patients for thrombosis is difficult as routine coagulation assays are insensitive to hypercoagulability. Platelet-derived microparticles (PDMP) are highly procoagulant and have been associated with various thrombotic conditions in humans. Measurement of PDMP may be useful to identify sick horses at-risk for thrombosis.

Objective: To develop a flow cytometric assay for measurement of equine PDMP and assess their contribution to thrombin generation in vitro.

Methods: Blood was collected into citrate anticoagulant from healthy horses (n=15). Platelet-poor plasma (PPP) and Microparticle (MP)-rich pellets with MP-depleted plasma were obtained from whole blood (WB) by low- and high-speed centrifugation, respectively. PDMP were identified in WB and PPP with flow cytometry by their size (< 1 um) and positive fluorescence for CD61 and Annexin-V. Thrombin generation was measured in PPP, MP-depleted plasma and MP-depleted plasma reconstituted with MP-rich pellets with a fluorogenic thrombin-specific substrate.

Results: Few PDMP were identified in WB and PPP from healthy horses by flow cytometry. Little thrombin was generated in MP-depleted plasma but thrombin generation was restored by reconstitution of MP-depleted plasma with MP-rich pellets. Horses could be grouped into low and high thrombin generators.

Discussion: PDMP can be detected by flow cytometry in equine blood, with few PDMP being present in WB or PPP from healthy horses. MP are required for in vitro thrombin generation in horses. Healthy horses show inherent variability in thrombin generation.
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THERAPEUTIC SERUM CONCENTRATIONS OF TRANEXAMIC ACID AND AMINOCAPROIC ACID IN DOGS

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Project Mentor: Daniel J. Fletcher

Introduction: Shock and trauma induce hyperfibrinolysis, increasing the risk of bleeding even in the absence of coagulopathy. The anti-fibrinolytic agents tranexamic acid (TEA) and L-aminocaproic acid (EACA) have the potential to reduce blood loss in dogs. Using thromboelastograms (TEG) and an in vitro model of hyperfibrinolysis, therapeutic plasma concentrations of EACA in adult and neonatal humans have been determined. There is evidence that dogs are hyperfibrinolytic compared to humans, suggesting that altered dosing may be needed in canine patients. We hypothesized that therapeutic serum concentrations of TEA and EACA would be higher in dogs than in humans.

Methods: Concentrations of EACA from 30 μg/ml to 500 μg/ml, and TEA ranging from 2.5 μg/ml to 160 μg/ml, were added to pooled citrated plasma from 7 research dogs and commercially available human citrated plasma. Hyperfibrinolysis was induced with 1000 U/ml tissue plasminogen activator (tPA), and kaolin activated thromboelastograms (TEG) were performed in duplicate. Therapeutic serum concentrations were defined as the minimum required for 0% estimated percent lysis (EPL) 30min after achieving maximum amplitude (MA).

Results: Therapeutic concentrations of EACA in humans and dogs were 126.3 μg/ml (95% confidence interval [CI], 91.1-161.2) and 556.3 μg/ml ([CI], 383.7-728.9), respectively. Therapeutic concentrations of TEA in humans and dogs were 14.8 μg/ml ([CI], 12.8-16.90) and 154.7 μg/ml ([CI], 110.8-198.7), respectively.

Conclusion: These results support the concept that dogs are hyperfibrinolytic compared to humans, and that higher doses of EACA and TEA may be required to inhibit fibrinolysis.
Current Position: Resident, Clinical Nutrition – 2nd year

THE RELATIONSHIP BETWEEN SERUM ADIPOKINES AND INSULIN WITH SERUM LONG-CHAIN POLYUNSATURATED FATTY ACIDS IN LABRADOR RETRIEVERS

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Project Mentor: Joseph J. Wakshlag

Obesity has been associated with an increased inflammatory response and insulin resistance due to adipose tissue-derived adipokines including increases in C-reactive protein (CRP) and leptin, and decreases in adiponectin in humans and rodents. Dogs appear to be similar with the exception of adiponectin, which may not be affected by obesity status. Serum long-chain polyunsaturated fatty acid concentrations have been positively and negatively associated with serum adipokines.

The aim of the study was to examine the relationship between leptin, CRP, adiponectin, and insulin to body condition score (BCS), serum lipoprotein eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid (AA) as a reflection of diet in one breed, the Labrador retriever.

Seventy-seven Labrador retrievers were evaluated for BCS, percent fasting serum lipoprotein fatty acid concentrations by HPLC, and leptin, adiponectin, insulin and C-reactive protein with ELISA’s. A multivariable general linear model was performed to examine each adipokine and insulin as dependant variables with independent variables of BCS, EPA, DHA and AA.

Increasing fasting serum leptin (P>0.01) and insulin were (P>0.01) positively associated with BCS. CRP and adiponectin were not associated with BCS. Increasing serum adiponectin was associated with decreased DHA (P = 0.01) and increased EPA (P=0.05) in serum.

Evidence suggests that obesity leads to a more pro-inflammatory adipokine profile and insulin resistance, while serum EPA may influence serum adiponectin concentrations when adjusted for serum DHA and AA. Omega-3 fatty acids, particularly EPA, may play an important role in the chronic inflammation of obesity by increasing serum adiponectin.
The objective was to examine the relationship between body condition status (BCS) on insulin sensitivity and serum adiponectin and adipose derived TNF-α and adiponectin. Two groups of 3 cows, BCS 4 and BCS 2, were enrolled. Glucose Tolerance Test (GTT; 0.25 g/kg BW) was performed 30 days before parturition and adipose tissue biopsies were collected before GTT. Serial glucose and insulins were measured to establish insulin and glucose area under the curve. Serum adiponectin status was assessed for low molecular weight and high molecular weight forms through immunoblotting. Omental and subcutaneous adipose samples were obtained to examine adiponectin, and TNF-a as markers of insulin sensitization.

Results: Serum glucose concentrations showed a significantly higher area under the curve for obese cows when compared to the lean cows (p <0.01). Insulin concentrations showed a trend towards increased area under the curve in obese cows. Omental and subcutaneous TFN-α was no different between the groups of cows. Adiponectin showed a 1 fold increase in expression in the omentum when compared to the subcutaneous adipose, which was not reflected in serum adiponectin. Lean cows had a significant increase in high molecular weigh adiponectin (p <0.05)

Conclusion: Obesity induces mild insulin resistance and serum adiponectin changes that reflect a loss of HMW adiponectin. Omental and subcutaneous fat biopsies showed similar expression of TNF-α and tissue adiponectin does not reflect the serum adiponectin HMW pattern, which may play a role in energy balance during net transition period.
EFFECTS OF A SYNBIOTIC ON FECAL QUALITY, SHORT-CHAIN FATTY ACIDS CONCENTRATIONS, AND THE MICROBIOME OF HEALTHY SLED DOGS

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Project Mentor: Joseph J. Wakshlag

Sled dogs commonly suffer from diarrhea. There are limited field studies using synbiotics as a supplement to prevent or treat diarrhea. To examine alterations in fecal quality, short-chain fatty acids (SCFA), and the fecal microbiome, 20 clinically healthy training sled dogs were randomized into 2 cohorts (10 synbiotic-fed, 10 placebo-fed) for a 6-week prospective study. Fecal pH, tag-encoded FLX 16S rDNA amplicon pyrosequencing (bTEFAP), and fecal short-chain fatty acid (SCFA) concentrations were measured at baseline (10 days prior to the study) and after 2 weeks of treatment. Fecal scores for all dogs were assessed at baseline, and every day for 6 weeks after initiation of treatment. Statistical methods included Wilcoxon Signed Rank, Chi Square analysis, and multivariate linear regression. Alterations in the fecal microbiome were observed with the only significant difference between the two groups being an increase in Lactobacillaceae (P=0.039) in the synbiotic-fed group after 2 weeks of treatment. A positive correlation was found between Lactobacillaceae and overall butyrate concentration (R=0.62, P=0.011) in all dogs. After 5 weeks of treatment, there was an improved fecal score and fewer days of diarrhea (X²=5.482, P=0.019) of the dogs in the synbiotic group compared to the placebo group, which coincided with a presumed contagious outbreak shared by all dogs in the study. Data suggest that the synbiotic used in this study results in a shift to a greater proportion of beneficial bacterial flora of the host colon, thereby decreasing the prevalence of diarrhea in training sled dogs.
Guppies in the Lab: Be Careful What You Ask For

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Cornell University MS (1) 2011-current

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Presented are results of a successful management change within a small aquatic laboratory after morbidity and mortality increases associated with Mycobacteriosis. Fish were initially obtained through another laboratory (later determined to have a high prevalence of Mycobacterium) as well as from wild populations in South America and were randomly distributed throughout the system as space became available. When Mycobacteriosis was confirmed in the colony, a decision was made to depopulate and completely clean the system.

Given the limited resources with number of tanks and amount of space within the laboratory, it was important to strategically place different types of fish to minimize the health risk to the overall colony. New animals were quarantined upon arrival. F1 and F2 generations were immediately removed from the parental tanks and raised within separate closed systems, thus decreasing the risk of horizontal transmission of disease. Since Mycobacterium tends to be more prevalent in aged animals, the oldest animals were routinely culled from the colony.

One year later, a follow-up sentinel screening was performed on animals from the colony. No evidence of Mycobacterial infection was observed based on both H&E and Ziehl-Neelsen acid-fast stained sections. This case highlights the importance of knowing the source of animals, diseases inherently present within a system, factors influencing susceptibility to diseases, placement of animals within a system, and benefits of sentinel screening.
MODULATION OF INNATE IMMUNITY BY A BACTERIAL PHOSPHOLIPASE

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Project Mentor: Hélène Marquis, Kirk Maurer

Listeria monocytogenes is an intracellular bacterial pathogen that causes disease in humans and animals. A mutant strain that has lost the ability to control the activity of a phospholipase C is attenuated in mice. This attenuation is not due to a lack of bacterial fitness, but appears to result from a modified immune response to infection. In a competitive assay, the mutant strain compromises the ability of wild-type (wt) L. monocytogenes to multiply in the liver of infected animals. To assess how the mutant modifies the hepatic immune response to infection, we monitored the kinetics of immune cell recruitment in the liver of infected mice and levels of serum inflammatory cytokines up to three days post-infection. Neutrophils peaked at day 1 post-infection in mice infected with wt strain, but did not increase in numbers at any time in the liver of mice infected with the mutant strain. Other innate immune cell types were recruited to the same levels in mice infected with either wt or mutant bacteria. Interferon gamma was detected in the serum of mice infected with wt bacteria at day 1-3 post-infection, but only at day 2 post-infection in mice infected with the mutant strain. Interleukin-12 was only detected in mice infected with wt bacteria. Also, transcriptional profiling of macrophages indicated that innate immunity signaling pathways were up regulated in wt but not in mutant infected cells at 6 hours post-infection. These results indicated that the phospholipase C of L. monocytogenes down-modulates the inflammatory response to infection.
DIAGNOSIS AND TREATMENT OF PARELAPHOSTRONGYLUS TENUIS INFECTION IN CAMELIDS: RETROSPECTIVE STUDY

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Aberrant migration of *Parelaphostrongylus tenuis* in camelids results in neurologic deficits, recumbency and sometimes death. Commercial screening tests for the diagnosis of *P. tenuis* are not available, making clinical signs and cerebrospinal fluid eosinophilia the primary means of antemortem diagnosis. The first objective was to determine the specificity of cerebrospinal fluid (CSF) eosinophil percentage for antemortem *P. tenuis* diagnosis. The second objective was to describe the clinical findings, treatment and outcome of camelids with *P. tenuis*. For objective 1, the specificity of CSF eosinophil percentage was determined in 37 camelids (1990-2010) diagnosed with *P. tenuis* or other neurologic condition based on postmortem examination. More than 17% eosinophils in CSF was 96% specific for diagnosing *P. tenuis* (AUC = 0.88; SE(AUC) = 0.065; P = 0.001). The second objective evaluated medical records of 68 camelids diagnosed with *P. tenuis* based on clinical signs and CSF eosinophilia (2000-2010). Camelids with *P. tenuis* had a median age of 3.5 years (1 month – 12 years) and 63% were females. Most cases (75%) presented during fall and winter. Hind limb ataxia (51%, 35/68) and recumbency (36%, 25/68) were common clinical signs. Treatment consisted of varied anthelmintic and anti-inflammatory regimens and data analysis to determine their effect on outcome will be presented. Only 12% (3/25) of recumbent compared to 44% (18/41) of ambulatory camelids survived 60 days after discharge. In summary, CSF eosinophil percentage is a specific diagnostic test for *P. tenuis* in endemic areas and a good treatment outcome can be achieved in ambulatory camelids.
Opioids are considered among the most effective drugs to control avian pain. However, the presence of exogenous opioids and metabolites in plasma does not demonstrate effective analgesia, as the required opioid binding receptors (OR’s) may not be present in the forebrain. Studies in the distribution of ORs in forebrains of mammals show a variety of different receptor type predominance across species. Studies indifferent avian species have illustrated that pharmacokinetics, metabolism, and analgesic effects of opioids also vary greatly. It is possible the variation in analgesia is due to the prevalence and distribution of different ORs in the CNS, which is unknown for the majority of bird species. The presence of opioid receptors in the avian forebrain has only been described in pigeons and chickens. Other avian species are thought to have mu, kappa and delta receptors considering clinical responses to opioid administration. The objectives of this study are to characterize CNS mu and kappa OR distribution in representative raptor, psittacine, anseriform, and passerine species using immunohistochemistry (IHC). Mu and kappa receptors were investigated being the most relevant for analgesia. The study included two phases: 1) Optimization of the IHC protocol for mu and kappa ORs using chickens, a species for which distribution of these receptors is known; 2) Characterization of mu and kappa receptor distribution in the defined avian species, using our validated IHC protocols. Distribution differences between species and neuroanatomic al locations were determined using the Chi-squared analyses. These differences are still being elucidated as this project is ongoing.
THE PRESENCE OF INTRAEPITHELIAL LYMPHOCYTES IN HEALTHY, HAIRIED SKIN OF DOGS AND ALPACAS

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A small population of resident T-lymphocytes is present in the healthy epidermis of the skin from humans, mice, cattle, and sheep. Resident lymphocytes were not found in the epidermis or adnexal epithelia of healthy skin from cats and horses. The purpose of the following two independent studies was to evaluate the presence of resident lymphocytes in the epidermis and adnexal epithelia of dogs and alpacas. This knowledge will be used to further aid the interpretation of these cells when viewed in skin biopsy specimens. One 6mm biopsy specimen from the normal skin of the dorsolateral thorax from 29 dogs was examined histologically and immunohistochemically for the presence of lymphocytes, CD3+ cells (T-lymphocytes) and Pax5+ cells (B-lymphocytes) in the epidermis and adnexal epithelia. All examinations were negative. It appears that lymphocytes rarely occur in the epidermis and adnexal epithelia of normal dog skin. Hence, the presence of lymphocytes in these structures in skin-biopsy specimens should be considered abnormal. In a separate study, one 6mm biopsy specimen from the normal skin of the dorsolateral thorax from 31 alpacas was examined histologically and immunohistochemically for the presence of lymphocytes, CD3+ cells (T-lymphocytes), and CD79a+ cells (B-lymphocytes) in the epidermis and adnexal epithelia. CD3+ T-lymphocytes – but not CD79a+ cells – were present in the epidermis and adnexal epithelia. Hence, the presence of lymphocytes in these structures in skin-biopsy specimens – in the absence of other signs of inflammation – should be considered normal.
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2009

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(1) Exotic Animal Medicine

PHARMACOKINETICS OF THE ANTI-EPILEPSY DRUG ZONISAMIDE IN DOMESTIC CHICKENS

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Project Mentor: R. de Matos

Traditional antiepileptic drugs (AED) appear to be safe in birds but not effective, with persistent seizures, inadequate blood levels and development of sedation reported. Zonisamide, a sulfonamide derivative AED, has been shown to be both safe and effective when used alone or as adjuvant therapy for treatment of drug resistant epilepsy in humans and dogs. Single, repeated and escalating dosing of zonisamide in domestic chickens was investigated. Several pharmacokinetic parameters including peak concentration ($C_{max}$), time to peak concentration ($T_{max}$), terminal half-life ($T_{1/2}$), area under the curve (AUC), clearance (Cl) and apparent volume of distribution (Vd) were determined. Dose-dependency, time (days) to achieve a steady state for each escalating dose and reported adverse effects will be described.
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<th>Institution and location (Chronological)</th>
<th>Degree</th>
<th>Year</th>
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<td>The Royal Veterinary College, UK</td>
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Current position: Resident, Imaging – 3rd year

(1) SA

OBSEVER AGREEMENT STUDY OF CERVICAL-VERTEBRAL RATIOS IN HORSES

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Project Mentor: Peter V. Scrivani

Objective: To quantify agreement and repeatability of cervical-vertebral ratio measurements.

Methods: An observer agreement study was performed using 75 horses with cervical neurologic signs. Measurements were made at C3–4 and C6–7 by a board-certified radiologist and an imaging resident. Intra and interobserver agreement was quantified using Bland-Altman plots. Repeatability was assessed by determining the mean and s.d. of duplicate measurements by the radiologist. We expect 95% of differences to be less than 2 s.d.

Results: At C3–4, the limits of agreement for the intra-vertebral ratio were between -5 and 4% for the intra- and -5 and 6% for interobserver comparison. For the intervertebral ratio, they were between -9 and 8% for the intra- and -10 and 10% for interobserver comparison. At C6–7, the limits of agreement for the intra-vertebral ratio were between -6 and 5% for the intra- and -6 and 8% for interobserver comparison. For the intervertebral ratio, they were between -7 and 7% for the intra- and -6 and 13% for interobserver comparison. At C3–4, all measurements were 95% repeatable (differences typically ≤4% and always ≤8%) for the intra-vertebral ratio and 96% repeatable (differences typically ≤8% and always ≤11%) for the intervertebral ratio. At C6–7, all measurements were 98% repeatable (differences typically ≤6% and always ≤7%) for the intravertebral ratio and 92% repeatable (differences typically ≤6% and always ≤10%) for the intervertebral ratio.

Conclusions: Cervical-vertebral ratios typically varied by 5–10% within and between examiners; awareness will reduce misdiagnosis of stenotic myelopathy.
Recent laryngeal neuropathy (RLN) is a major cause of poor athletic performance in Thoroughbred racehorses and sport horses. RLN results in progressive atrophy of the laryngeal muscles including the sole arytenoid abductor, the \textit{cricoarytenoid dorsalis} (CAD). Atrophy of the left CAD muscle results in loss of arytenoid cartilage abduction and dynamic airway collapse.

The goal of this study was to determine the relationship between geometry of the CAD muscle using transesophageal ultrasound (TEE), and laryngeal function at exercise, with the long term goal being earlier detection of the disease. Transesophageal ultrasound was performed in thirty-eight horses under light sedation and videoendoscope guidance. The probe was advanced to image the left CAD muscle through the esophageal wall. A full inspection of the muscle was performed and then the cross-section of the midbody of the CAD muscle was measured. This was repeated on the right CAD.

Data was obtained from 38 horses (16 geldings, 12 mares, 10 colts, 13 Thoroughbreds, 25 Standardbreds). The distribution of exercising laryngeal grades was 27 grade A (full abduction), 4 grade B (partial collapse), 7 grade C (complete collapse). There was a progressive decrease in the thickness of the left CAD muscle with worsening exercise grade (grade A, 12.0 ± 0.4 mm; grade B, 12.5 ±1.3 mm; grade C, 10.8 ±1.1 mm). The ratio of left:right CAD thickness was significantly different between horses with abnormal exercising grades and those with normal laryngeal function at exercise (grade A, 0.97 ±0.03; grade B, 0.72 ± 0.03; grade C, 0.72 ±0.02, p<0.05).

These data suggest that transesophageal ultrasound may be a valuable tool for detecting laryngeal muscle atrophy. Further work is needed to determine the predictive function of this technique.
CORRELATION OF MRI UTE IMAGING WITH MULTIPHOTON MICROSCOPY IN THE EVALUATION OF MENISCAL REPAIR

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Project Mentors: Drs. Lisa Fortier and Hollis Potter

Introduction: Magnetic resonance imaging (MRI) is a non-invasive imaging modality commonly used to evaluate soft tissues of joints. Visualization of the menisci remain challenging since the highly ordered collagen environment causes rapid decay of the MRI signal, resulting in a hypointense appearance when using traditional pulse sequences. Ultra-short echo time (UTE) MRI is a method to quantitatively image tissues with rapid signal decay, such as the meniscus.

Methods: Standard morphologic and UTE images were acquired from sheep with surgically created tear-repairs at various stages of healing. The MRI signal decay constant T2* was calculated from the UTE data, and color-coded T2* maps were generated. T2* data from repaired and native menisci were compared to corresponding data from multiphoton microscopy (MPM). MPM evaluated the normalized second harmonic generation signal intensity (SHG-SI) and structure autoflorescence (AF), which demonstrate fibrillar collagen content and collagen crosslinking, respectively. The SHG images were evaluated to measure tissue heterogeneity, with high autocorrelation values (ACD) indicating greater homogeneity.

Results: Significant differences of SHG-SI (p=0.04), AF (p=0.03), and ACD (p=0.02) were found between menisci with tears and the native meniscus, indicating reduced collagen content, reduced collagen crosslinking and greater heterogeneity associated with meniscal tears. Significant correlations were found between meniscal T2* and SHG-SI (r=-0.53, p=0.03) and AF (r=-0.54, p=0.03).

Discussion: Meniscal T2* values correlated with MPM measures of meniscal collagen organization, demonstrating greater disorganization in menisci with repaired tears. MPM measurements support UTE T2* data to measure meniscal integrity.
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EFFECTS OF BILATERAL HYPOGLOSSAL NERVE BLOCKADE AND STIMULATION, AND HYOID MUSCLE STIMULATION ON RADIOGRAPHIC LARYNGEAL POSITION IN THE RESTING HORSE

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The hypoglossal nerve and the muscles it innervates are important in swallowing and maintaining laryngeal position. Dysfunction of the structures can result in obstructive sleep apnea, dysphagia, and a naturally-occurring disease in horse which produces an expiratory obstruction at exercise. We hypothesized that hypoglossal nerve block would result in laryngeal descent and that stimulation of the thyrohyoid, geniohyoid muscles, and/or the hypoglossal nerve separately or in combination would produce laryngeal elevation and anterior displacement. The positions of the larynx and basihyoid bone were evaluated radiographically. Laryngeal position was assessed in sixteen horses before and after bilateral hypoglossal nerve block with local anesthesia. Stimulation effects were studied after surgically implanting electrodes in five additional horses in the thyrohyoid muscles; two of these horses also had electrodes placed in the geniohyoid muscles; and two others had a nerve cuff electrode placed around the hypoglossal nerve allowing us to explore the results of hyoid muscle stimulation on laryngeal position.

Hypoglossal block produced no significant change in laryngeal position. Hypoglossal nerve stimulation produced significant anterior movement of the larynx. Thyrohyoid muscle stimulation produced significant laryngeal elevation. As shown by performing a paired Wilcoxon Signed Rank test, combining hypoglossal nerve stimulation with thyrohyoid stimulation produced significant dorsal and anterior movement of the larynx. Electrical stimulation of the hypoglossal nerves and selected hyoid muscles produced laryngeal advancement and elevation. The horse may be a useful preclinical model to study the effects of electrical stimulation on laryngeal position.
The objective of this study is to compare in-situ contractile response, mechanical integrity, and histomorphologic characteristics of reconstructed skeletal muscle tissue using various mesh material in the abdominal wall of Wistar rats (*Rattus norvegicus*). Once these rats were anesthetized with isoflurane, a 1.2cm x 1.2cm partial-thickness muscular defect was made by excising the external & internal oblique layers of the ventral lateral abdominal wall while the underlying transverse abdominus & peritoneum remained intact. The created defect was covered with a mesh material and sutured in place at all four corners of the mesh. Three different kinds of mesh were tested and identified as mesh A, B, and C. The selection of mesh for surgery was randomized. In order to reduce the number of animals used, the defect was created bilaterally about 1cm away from the linea alba. The rats were humanely euthanized at 2, 4, and 12 weeks after surgery to collect tissue samples. The individual performing in-situ testing was blind to the identity of the mesh. Results of the in-situ tests revealed that mesh A was superior to both meshes B and C in terms of titanic and twitch force at all three time periods. At 2 weeks, Mesh A resembled the mechanical strength of native tissue more closely than both meshes B and C. This study provides objective parameters to identify an appropriate mesh material to repair pelvic hernias as well as reduce the post-operative complications commonly observed in clinical cases.