New Directions in Diagnosis and Treatment of Canine Acute Pancreatitis

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Declaration

I declare that this thesis is my own account of my research unless specifically stated and contains as its main content, work which has not previously been submitted by me for a degree at any tertiary education institution.

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Abstract

Acute pancreatitis is an important disease in companion animal medicine, and diagnostic methodology available to veterinary practitioners is often limited. Evidence based principles for the management of this common disease are also lacking. This thesis explores the current diagnostics of canine pancreatitis and management of this condition, reviewing the literature across both the veterinary and human medical fields.

Assessment of the specificity of canine pancreatic-specific lipase (cPL) was made in a post-mortem study and calculated to be 82-92%, with a correlating sensitivity of 45-55%. A multi-centre study of dogs presenting with clinical signs consistent with acute pancreatitis to assess a new laboratory test, serum canine pancreatic elastase-1 (cPE-1) was also performed. This test had a sensitivity ranging from 66-79%, with a specificity of 92%. The sensitivity of both laboratory tests was greater in dogs with severe disease.

To assess potential treatment options, a clinical severity score was established, with gut health, respiratory complications, cardiac complications, and blood pressure determining the final score. Retrospectively, plasma administration did not appear to be associated with treatment success, but this conclusion was limited by the retrospective nature of the study and small numbers of dogs. Out of the other factors, fasting for 3 or more days was the one most significantly associated with mortality. To begin assessment of nutritional modalities, pancreatic responses in healthy dogs to varying dietary fat composition (ranging from 4%DW to 16% DW) was assessed, with no statistical difference determined. On the basis of this, a pilot study of 10 dogs with severe pancreatitis was undertaken, with 5 dogs fed enterally and another 5 dogs were given total parenteral nutrition (TPN). No differences in mortality or days of hospitalisation between the two were found, but there were significantly less episodes of vomiting or regurgitation in the dogs given food ($p < 0.001$). There were also more

severe complications (4/5) in the TPN group compared to the enteral feeding group (2/5).

In all, this thesis supports the new premise of enteral feeding of dogs with acute pancreatitis early in the course of disease, determines the sensitivity and specificity of two diagnostic tests and has established an objective marker of disease severity.

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Introduction

Pancreatitis is an important disease of dogs. Acute pancreatitis can cause profuse vomiting with resultant dehydration and hypovolaemia (Simpson, 1993; Williams and Steiner, 2005). There is a high mortality rate associated with systemic effects of the disease, and dogs often require intensive treatment and hospitalisation (Ruaux and Atwell, 1998b).

Predicting which animals will develop severe complications is difficult, although there is a significant association between fatality and existence of concurrent diseases such as diabetes mellitus, hyperadrenocorticism, and epilepsy (Cook et al., 1993; Hess et al., 1998; Ruaux and Atwell, 1998b). Traditional biochemical methods of diagnosing pancreatitis such as elevation of serum amylase and lipase concentrations are poor predictors of mortality (Mansfield et al., 2003). Despite an increase in the number of studies in the past decade addressing the diagnostic difficulties faced in canine pancreatitis, it is still unclear how sensitive and specific the currently used diagnostic modalities are. Part of this difficulty is a lack of a true gold standard, as pancreatic histopathology is seldom performed in severely unwell dogs with pancreatitis. It is also uncertain as to how the pancreatic inflammation seen histologically correlates to clinical severity, or indeed if it is the primary reason for presentation of the animal.

Treatment of acute pancreatitis is non-specific and aimed at correcting secondary consequences of the disease (such as hypovolaemia or pain for example) rather than directly treating the pancreatic inflammation. There is a lack of controlled studies in treatment of this condition, and most recommendations are extrapolated from animal experimental models and human gastroenterology. An important aspect of developing any prospective treatment trials is to ensure that animals of equal clinical

severity are compared in studies, in order to ensure that any benefits are due to the treatment intervention rather than the study population.

Purpose

This body of work aims to answer the following questions

- In a cohort of dogs who display clinical signs that could be consistent with canine pancreatitis, what is the specificity and sensitivity of serum canine pancreatic-elastase 1, a potentially new diagnostic test?
- In a sufficiently large cohort of dogs with diseases of similar severity to acute pancreatitis, what is the clinical specificity and sensitivity of canine pancreatic lipase?
- Is there an effective and robust way to characterise the clinical severity of canine pancreatitis to aid in the development of future research into optimisation of treatment strategies?
- Does the administration of plasma or minimal enteral nutrition have any potential benefits in the treatment of acute pancreatitis?
- Does differing fat content of diet cause differing responses of the canine pancreas, and necessitate specific nutritional strategies?
- Is early interventional enteral nutrition delivered proximal to the pylorus well tolerated by dogs with acute pancreatitis?
- Is there evidence that early interventional enteral nutrition may be of benefit in treating dogs with severe acute pancreatitis?

List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
APN	Acute pancreatic necrosis
CCK	Cholecystokinin
CI	Confidence Interval
CIRCI	Critical illness related corticosteroid insufficiency
CRP	C-reactive protein
ELISA	Enzyme-linked Immunosorbent Assay
EN	Enteral nutrition
ERCP	Endoscopic Retrograde Cholangiopancreatography
FFP	Fresh frozen plasma
ICAM	Intercellular adhesion molecule
IL	Interleukin
IV	Intravenous
MEN	Minimal (micro) enteral nutrition
MMP	Matrix metalloproteinases
MODS	Multiple organ dysfunction syndrome
NF-κB	Nuclear factor kappa B
NG	Nasogastric (delivery of EN)
NJ	Nasojejunal (delivery of EN)
NO	Nitric oxide
NOS	Nitric oxide synthase
NPV	Negative Predictive Value
PE-1	Pancreatic Elastase-1
PLA	Phospholipase
PLI	Pancreatic lipase immunoreactivity
PMN	Polymorphonuclear leukocytes
PN	Parenteral nutrition
PPN	Partial parenteral nutrition
PPV	Positive Predictive Value
PSTI	Pancreatic secretory trypsin inhibitor
RIA	Radioimmunoassay
ROC	Receiver operator characteristics
ROS	Reactive oxygen species

RT-PCR	Real-time polymerase chain reaction
SAA	Serum amlyoid A
SIRS	Systemic inflammatory response
Spec-cPL	Specific canine pancreatic lipase
TAP	Trypsinogen activation peptide
TLI	Trypsin-like immunoreactivity
TNF	Tumour necrosis factor