SIS12

Changing our Ideas in the Diagnosis and Treatment of Pancreatitis

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Objectives of the Presentation

This seminar will present updated information on acute pancreatitis in the dog. Included is newer information on the diagnosis and treatment of pancreatitis. Included are therapies for pain, antiemetics and nutritional management.

General Key Points

- Most dogs with pancreatitis have vomiting, abdominal pain and lethargy.
- Vomiting is controlled with pain management and antiemetics.
- Nutritional management is important for severe cases.

Key Clinical Diagnostic Points

- Serum PLI test is the most accurate test for the diagnosis of pancreatitis.
- Ultrasound changes supports the diagnosis.
- Amylase and lipase is unreliable for the diagnosis of pancreatitis.

Key Etiologic and Pathophysiologic Points

- Pancreatitis begins intracellularly with activation of pancreatic enzymes.
- Local pancreatic inflammation ranges from edematous to necrotic changes.
- Systemic disease results from cytokine release in pancreatitis.

Key Therapeutic Points

- Fluid and electrolyte replacement is important.
- Pain management is indicated in all cases.
- Antiemetics using NK1 antagonists is indicated for vomiting.
- Oral nutrition is indicated when vomiting is controlled.

Key Prognostic Points

- With systemic manifestations of pancreatitis the prognosis becomes guarded.

Overview of the Issue

The incidence of pancreatitis characterized by significant histological changes identified at necropsy in cats and dogs range from 1.3–1.5% respectfully. This is where the similarities diverge. Most dogs have acute pancreatitis while most cats have chronic pancreatitis. Clinical presentation and diagnostic criteria differ as well between species and type. Acute pancreatitis is potentially reversible but can also be fatal while chronic pancreatitis has irreversible changes and rarely fatal. The following will deal with the latest information on acute forms of pancreatitis in the dog and cat.

The pancreas secretes high quantities of enzymes required for digestion of a meal. If these enzymes become activated within the pancreas serious damage to the organ will take place. Under normal conditions autodigestion does not take place due to a number of protective mechanisms. Enzymes produced by the pancreas are secreted, as zymogens and these zymogens or proenzymes must become activated prior to being functional. Normal enzyme activation takes place only in the intestine. It is generally believed that pancreatitis develops when there is activation of digestive enzymes within the gland and subsequent autodigestion. The location of the initiation of enzyme activation is thought to begin at the intercellular level with abnormal zymogen activation. Studies have indicated that there is an

abnormal secretory process of zymogen granules their subsequent fusion with lysosomes. Lysosome enzymes then activate trypsinogen that begins the autodigestive process.

Other observations suggest that the depletion of acinar glutathione in the pancreas may stimulate oxidative stress and that contributes to tissue injury. Disturbances in glutathione, a tissue antioxidant, may alter zymogen protein processing, impair zymogen transport and assist in activation of pancreatic enzymes. In animals, superoxide dismutase and catalase treatment reduced experimental pancreatitis and suggest that antioxidant therapy started early in the course of pancreatitis may be of benefit.

Once there is activation of trypsinogen all zymogens become activated. Damage is amplified by elastase and phospholipase. The proteases will activate the kinin, coagulation, fibrinolytic and complement cascades. Local complement activation induced by certain toxins or from local ischemia to the pancreatic microcirculation may play a role in initiating the cascade of events.

Experimental studies suggest that the severity of acute pancreatitis is determined by the degree of either pancreatic ischemia or the amount of protease-inhibitor imbalance. Released proteases normally bind to alpha1-protease inhibitor that is then transferred to alpha 2 macroglobulin. This complex is then removed from the plasma by the reticuloendothelial system. Experimental studies in dogs have show that once alpha2-macroglobulins become depleted death soon ensues emphasizing that once this protective system becomes saturated, proteolytic enzyme damage proceeds aggressively. Associated with the systemic inflammatory response is the release of C-reactive protein from the liver as an acute phase response protein. It appears that elevations in C-reactive protein may correlate with the severity of the pancreatitis but as yet not proven to be a prognostic indicator.

Clinical Conditions

There is much confusion and controversy regarding the pathogenesis, diagnosis and treatment of acute pancreatitis in the dog. The spectrum of clinical disease can range from mild signs to those which are fulminate and frequently fatal. The discussion of medical management in this section will cover the more complex cases of acute pancreatitis in the dog.

In most all cases of pancreatitis the etiology is never determined. In many cases nutrition becomes a factor associated with pancreatitis. The ingestion of high fat diets especially in the obese patient is a well-accepted etiology. Hyperlipoproteinemia is also common in pancreatitis. Whether or not this is a result of fat necrosis secondary to the pancreatitis or the cause of it is unknown. It is postulated that high concentrations of triglycerides become activated by pancreatic lipase and produce pancreas. Pancreatitis is common in Schnauzers that have primary hyperlipidemia. A number of drugs are also shown to cause pancreatitis and include thiazides, furosemide, tetracycline, L asparaginase and azathioprine. The role of corticosteroids as a cause of pancreatitis is suggested but as yet unproved and is still controversial. Other factors include the reflux of duodenal fluid into the pancreatic ducts (in cats) and conditions that may result in obstruction of the pancreatic ducts. Parasites, calculi, surgery, tumors and inflammation are potential causes of ductular obstruction. Hypercalcemia secondary to hyperparathyroidism is a reported etiology of pancreatitis in humans and has been associated with clinical pancreatitis in dogs. Additional important factors associated with clinical pancreatitis include trauma and factors causing local pancreatic microcirculatory ischemia. Blunt abdominal trauma and surgical trauma are the common associations in animals. Shock and gastric dilation-volvulus syndrome are examples of pancreatic ischemia and has been associated with a secondary pancreatitis. This latter mechanism is felt to be secondary to ischemia with reperfusion injury.

In a study of 70 dogs confirmed having pancreatitis certain risk factors were identified. It was concluded that the breed, overweight body condition, small breed size, prior gastrointestinal diseases, diabetes mellitus, hyperadrenocorticism and hypothyroidism are at risk for developing acute pancreatitis. No concurrent medications, glucocorticoid therapy, anesthesia or trauma were at increased risk. Dogs with surgery in the two weeks prior had more pancreatitis than the control population in this study. The breeds at most risk were Yorkshire terriers, toy poodles and miniature Schnauzers.

Acute pancreatitis is one of the most difficult diseases to diagnose and there is no one diagnostic test having a very high sensitivity for pancreatitis. One must have a degree of suspicion based on the risk factors listed above and the clinical findings however the signs can be quite variable. Acute or chronic

vomiting is a major clinical sign associated with pancreatitis. The clinical spectrum can vary dramatically from case to case. In a study of 70 dogs with severe pancreatitis, vomiting (90%), weakness (79%), abdominal pain (58%), dehydration (46%), and diarrhea (33%) was reported. Severe cases had systemic clinical signs such as fever or even cardiovascular shock.

Diagnosis

Laboratory findings are quite variable and to some extent parallel the severity of the clinical disease. Leukocytosis is usually present and represents the inflammatory nature of the disease. The biochemistry profile will show variable changes. Azotemia may occur secondary to dehydration however acute renal failure from acute tubular necrosis can also be present. Elevated liver enzymes are also expected in pancreatitis. Increases in ALT, AST and ALP are most often observed. In experimental pancreatitis in dogs histological evidence secondary hepatopathies occurred in all cases. Occasionally partial or complete blockage of the common bile duct from periductal inflammation can result in icterus with increases in total bilirubin concentrations. Hyperglycemia and hypokalemia may also be present. Acid base changes are quite variable. Severe cases may have a marked acidosis however severe vomiting can also result in a metabolic alkalosis. When DIC and coagulopathies occur it generally reflects a poor prognosis.

Amylase and lipase have been used for years to diagnose pancreatitis in the dog. Unfortunately they are not consistently reliable. The specificity of both of these parameters only approximates 50%. Factors such as azotemia will increase serum amylase and lipase due to decreased renal removal and dexamethasone and prednisone will increase serum lipase levels. Further complicating matters is that both amylase and lipase are found in a number of other organs that will contribute to total measurement. Decreased concentration of trypsin-like immunoreactivity (cTLI) is specific for the diagnosis of exocrine pancreatic insufficiency in the dog. Elevated cTLI concentrations can occur in pancreatitis but the sensitivity of serum cTLI concentration for pancreatitis in dogs is around 35% making it a poor test to diagnose pancreatitis. Amylase and lipase are essentially worthless tests for the diagnosis of pancreatitis in the cat and fTLI although better, also has its limitations.

Recently, a new test has become available for the diagnosis of pancreatitis in the dog and cat; pancreatic lipase immunoreactivity (cPLI and fPLI). The advantage of this test is that a number of organs synthesize and secrete lipases but PLI measures lipase that only originates from the exocrine pancreas. The sensitivity of cPLI for the diagnosis of pancreatitis in the dog is reported to be approximately 80% in one small series and even higher for fPLI in cats. Data would suggest that serum cPLI can be used as a diagnostic test for pancreatitis even in dogs with renal failure and prednisone does not have any effect cPLI values. cPLI is available at the GI Lab at TAMU and IDEXX has a similar Spec cPL™ for the diagnosis of pancreatitis. fPLI is currently only available at TAMU.

Abdominal radiographs may reveal increased density, diminished contrast and granularity in the right cranial abdomen with displacement of the stomach to the left and widening of the angle between the stomach and the duodenum. A non-homogenous mass and loss of echodensity in the area of the pancreas is often noted on ultrasonographic examination. One study found the sensitivity of ultrasound to be 68% but this varies based on operator skill. We will frequently perform a fine needle aspiration of suspected areas of pancreatitis and finding cytology showing suppurative inflammation helps support the diagnosis.

We also find abdominocentesis to be very helpful if effusion is present. Suppurative non-septic inflammation is the typical finding and is rarely septic. Recently we have combined abdominal fluid analysis with measurement of abdominal fluid lipase concentrations. Finding the abdominal lipase concentration markedly higher than serum lipase supports the diagnosis of pancreatitis in many cases. A negative abdominal paracentesis but with radiographic or ultrasound evidence of effusion a diagnostic peritoneal lavage is indicated.

Finally biopsy provides the definitive diagnosis. Surgery and laparoscopy are two options to consider for biopsy. Although acute pancreatitis is not considered to be a surgical condition indications for surgery would include septic peritonitis, pancreatic abscess or to place a feeding tube in the patient suspected of having.

Treatment

Treatment of pancreatitis is supportive and should be tailored for the individual case. Basic therapy involves correction of fluid and electrolyte imbalance, nutritional considerations, pain management and the control of secondary complications. The material in the following section deals with the management considerations for the severe and often life-impending acute pancreatitis case. Mild cases of pancreatitis may require minimal or only a portion of the recommendations included below.

Pancreatic rest in the form of fasting is the traditional recommendation for any patient with pancreatitis by giving nothing per os (NPO) for three to four days. The belief is that feeding results in the release of pancreatic secretagogues that will stimulate pancreatic secretions and exacerbate the pancreatitis. Short term fasting is probably justified in patients that vomit and are predicted to resolve in a few days. There is however little evidence to justify placing patients NPO that do not vomit. Current literature suggests that feeding a patient with acute pancreatitis does not further stimulate pancreatic secretions in the already inflamed pancreas. Vomiting or pain associated with eating would be reasonable reasons to fast patients. (See below for nutritional management considerations.)

Fluid and electrolyte therapy is given in virtually every case of pancreatitis. The effects of fluid loss into the peritoneal cavity and vomiting losses coupled with the vasoactive factors released from the pancreas produce a hypovolemic or possibly endotoxic shock. Fluid losses through vomiting may also result in a hypochloremic metabolic alkalosis. Most cases however usually have a metabolic acidosis with depletion of total potassium stores. A balanced electrolyte solution such as Normosol supplemented with additional potassium is indicated in most all cases. Careful monitoring of electrolyte concentrations and patient hydration and renal output is essential in the severe pancreatitis case.

The role of plasma replacement for pancreatitis is not well documented. When protein levels decline plasma therapy would seem reasonable for maintaining blood volume and perfusion. If plasma is not available colloids may be of benefit in improving microcirculation. With severe pancreatitis there is also consumption of plasma protease inhibitors and plasma replacement will help replenish these as well. Recent studies in the dog fail to support this hypothesis. The most benefit of plasma might be for the replacement of clotting factors.

Antibiotics should be considered for the severe case or whenever there is evidence of sepsis. Infectious complications of pancreatitis are rare in dogs and prophylactic use of antibiotics is always to be questioned. In one experimental pancreatitis study in dogs antibiotic therapy improved survival. Broad-spectrum antibiotics effective against aerobes and anaerobes should be given. I generally place my severe pancreatitis cases a second-generation cephalosporin or a combination of ampicillin and enrofloxacin for this purpose.

Antiemetics are given if the vomiting is severe and there is significant fluid loss from vomiting. Metoclopramide is given for antiemetic effects and to improve gastrointestinal tone (0.2–0.4 mg/kg QID PO or SC, or 0.01–0.02 mg/kg/hr constant rate infusion). Anticholinergic agents are not indicated because of the profound effects on GI motility. Alternative antiemetics include chlorpromazine (0.05 mg/kg IV or 0.5 mg/kg IM tid to QID) a broad-spectrum antiemetic but because of its arterial dilatory effects this drug should not be given until there is adequate volume expansion. With refractory vomiting ondansetron (Zofran™ 0.1mg/kg BID to TID IV slowly over 2–5 minutes) or dolasetron (Anzemet™ 0.6–3.0 mg/kg daily IV) can be used but both are expensive. Most recently maropitant (Cerenia™) is a NK1 inhibitor, and is most effective in controlling vomiting and is my treatment of choice.

Analgesics should be considered in all patients with pancreatitis even if there is no outward evidence of abdominal pain. For mild pain meperidine hydrochloride (5–10 mg/kg IV, IM prn) or butorphanol tartrate (0.1–1.0 mg / kg SC q 1 to 6 hr.) is suggested. Other considerations include transdermal fentanyl patch that maintains effective plasma concentrations of fentanyl providing continuous anesthesia for up to three days. The patch is applied to the skin that has been clipped usually over the dorsal neck or rump and then bandaged to prevent dislodgment. Patches are available in four sizes, delivering 25, 50, 75, or 100 µg/hour. Empirically, small dogs (<10 kg) receive a 25 µg patch, medium dogs (10–29 kg) receive a 50 µg patch and large dogs (>30 kg) receive a 75 µg patch. Small dogs or cats may receive a half of a 25 µg patch.

With moderate pain fentanyl is given as a continuous infusion (3–5 µg/kg/hr). With severe pain we increase the dose of fentanyl (5–10 µg/kg/hr and add ketamine (0.2–0.4 mg/kg/hr constant rate infusion. The animals should be monitored for side effects particularly respiratory depression.

We have treated some patients having severe abdominal pain with some success using intrathoracic placement of local anesthesia. Lidocaine (1.5 mg/kg) followed by bupivacaine (Marcaine 1.5 mg/kg). The lidocaine is given first for rapid action and because bupivacaine is initially painful. Following the injections the dog is placed on their back so the anesthesia will drain into the area of the vagal nerves. We generally use a butterfly catheter for the injection and given as needed for control of the pain before systemic analgesics kick in. Some have recommended intra-abdominal local anesthesia.

Nutritional supplementation in severe pancreatitis is very important. Studies have shown adequate nutrition to improve survival in experimental pancreatitis. If the patients are not predicted to be eating on their own within 3–4 days nutritional support indicated. The type and route of administration is still controversial. Partial or total parenteral nutrition (PPN or TPN) has been used with pancreatitis and this route does not stimulate pancreatic enzyme secretion. The expense, difficulty in administration and complications of sepsis are of concern with parenteral feeding.

It has been shown that enteral feeding of elemental diets or polymeric diets (e.g., Clinicare™) via jejunostomy feeding tube does not significantly increase pancreatic exocrine secretions and has the advantage of being easier to perform, prevents intestinal mucosal atrophy and bacterial translocation that accompany fasting or parenteral nutrition. Jejunostomy tube feeding also does not appear to stimulate significant pancreatic enzyme secretion. Jejunostomy feeding tube placement requires surgery or laparoscopy. Alternatively "J" tubes can be placed endoscopically using a Cook Jejunal Feeding tube set™. Some have suggested adding pancreatic enzymes to the enteral feeding but the benefit is unknown. Gastrostomy feeding tubes can also be used if vomiting is not a major problem.

When beginning to feed orally the diet should be a carbohydrate-rich and low-fat diet given as small frequent meals. A final recovery diet is then prescribed that is low in fat content.

Unproven therapy should be considered only after careful evaluation of the individual case. The use of corticosteroids may be indicated in immediate management of septic or hypovolemic shock but as a role as an anti-inflammatory agent for pancreatitis it is not indicated. Attempts to reduce pancreatic secretion by using atropine, glucagon, antacids, cimetidine or other acid blockers or nasogastric suctioning are also of unproved benefit in human studies.

DIC is a complication of severe acute pancreatitis. In patients with severe pancreatitis and with a suspicion that DIC as a complication heparin 120 units/kg SC tid is a recommended. Heparin may also prevent microclot formation in pancreatitis as well. One can also add the first dose of heparin to a plasma transfusion and administer it IV.

Somatostatin, a hormone that decreases pancreatic secretion, has also been proposed as a therapy. Experimentally, somatostatin will reduce severity of pancreatitis in dogs when given before induction of pancreatitis. The benefit after the onset of pancreatitis is of questionable value in experimental animals and in human patients.

Because oxidative damage is thought to be the result of cellular membrane death antioxidants may be of benefit in the acute management of cases. Studies show that perfusion of the pancreas with free radical scavengers ameliorate the severity of pancreatitis in experimental canine models. Vitamin E is a potent membrane antioxidant and SAMe replaces glutathione stores that may have some benefit in pancreatitis.

Peritoneal lavage removes inflammatory products in the peritoneal cavity before they are absorbed. Problems encountered include tube placement, adequate fluid recovery, and bacterial contamination. Approximately 5–8 ml/kg of fluid is lavaged four times a day with a dwell time of one hour. Careful patient monitoring is critical in these patients. Alternative techniques include open peritoneal lavage performed during surgery.

Surgery is rarely indicated for pancreatitis. Surgery may be considered with obstructive jaundice, intestinal obstruction, and to treat a possible pancreatic abscess, cyst or intestinal perforation. It is however questionable if obstructive jaundice is an indication for surgery. We have had a number of patients with secondary bile duct obstructions recover over 3 to 4 weeks as the pancreatitis resolves.

Pancreatic enzyme supplementation has been reported to decrease the pain that accompanies chronic pancreatitis in humans by the feedback inhibition by endogenous pancreatic enzyme secretion. It is not known if enzymes are helpful in the acute cases but such supplementation may have some benefit in early nutrition of patients with acute pancreatitis.

Acute pancreatitis can vary in severity of signs and often results in multi-system involvement. Despite the extensive literature on the pathogenesis of pancreatitis and its complications, there have been very few advances made in the management of this disease. It is possible that future research on modification of enzymatic disturbances will result in an effective treatment for acute pancreatitis.

KEY DRUGS, DOSAGES AND INDICATIONS

Key Drug	Drug Class	Dose Range	Frequency	Route	Indications
Meperidine	Narcotic analgesic	5–10 mg/kg IV, IM PRN) or	PRN	IV/IM	Abdominal pain
Butorphanol tartrate	Narcotic analgesic	0.1–1.0 mg / kg	q 1–6 hr	SQ	Abdominal pain
Mariopitant	Antiemetic	1 mg/kg	q 24 hr	SQ	Vomiting
Ondansetron	Antiemetic	0.1 mg/kg	BID/TID	IV	Vomiting

SUMMARY

Once the etiology is identified appropriate therapy can be instituted. Since there are few clinical studies one should critically evaluate response and adjust treatment as needed.

REFERENCES

1. Porterpan B, Zoran D, Steiner JM: Serial serum pancreatic lipase immunoreactivity concentrations in a dog with histologically confirmed pancreatitis, *Vet Med* 2006; 101:170.
2. Steiner JM. Diagnosis of pancreatitis, *Vet Clin North Am Small Anim Pract* 2005; 33:1181.