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REVIEW ARTICLE

Review of feline pancreatitis part two: clinical signs, diagnosis and treatment

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In the past decade pancreatitis has become recognised as a significant disease in the cat. Chronic, mild pancreatitis is often associated with more commonly diagnosed diseases such as inflammatory bowel disease or cholangitis/cholangiohepatitis. Furthermore, acute pancreatitis with similar complications to those seen in dogs is now diagnosed more frequently in cats. Unfortunately, the clinical signs and clinicopathological findings in cats with pancreatitis are often non-specific and vague. The lack of specific signs often results in a diagnosis being made only when the veterinary surgeon has a strong index of suspicion for pancreatitis and vigorously pursues that diagnosis. Pancreatitis is an important disease in cats, has been implicated as a potential cause of diabetes mellitus, and when present complicates the treatment of diabetes and other intra-abdominal diseases in cats.

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Patient information

No significant age or sex predisposition has been found in reviews of pancreatitis in cats (Schaer 1991, Hill & Van Winkle 1993, Simpson et al 1994). Pancreatitis has been reported in cats with an age range from 5 weeks to 20 years of age (Steiner & Williams 1997). However, some authors feel that cats older than 7 years are more likely to be affected (Schaer 1991, Simpson 1993). Siamese cats have been reported to have an increased incidence of pancreatitis in two studies (Macy 1989, Hill & Van Winkle 1993). Hill & Van Winkle (1993) found that cats with suppurative pancreatitis were more likely to be cachectic than cats with necrotising pancreatitis. No studies have determined that significantly underweight or overweight cats are more likely to develop pancreatitis (Macy 1989, Schaer 1991, Hill & Van Winkle 1993).

Clinical signs

Pancreatitis in cats has been recognised only in recent years as the clinical presentation and history of affected cats is fairly ill defined and diagnosis is not easily based on clinical signs alone (Williams 1994). Experimental studies of acute pancreatitis induced by infusing oleic acid into the pancreatic duct in seven cats showed there were few significant findings on physical examination after the induction of pancreatitis (Kitchell et al 1986). Vomiting only occurred in two cats, and that was confined to a single episode in each animal. No diarrhoea developed in any of the cats.

Hill & Van Winkle (1993) performed a retrospective review of spontaneous acute pancreatitis in 40 cats. Thirty-eight per cent of the cats were presented with an acute onset of disease, while the remainder showed two distinct stages of progression. The initial stage was defined as a period of anorexia, lethargy and weight loss. This period was then followed by an acute deterioration with development of shock and obtundation despite aggressive intravenous fluid therapy. Most cats had evidence of cardiovascular dysfunction but very few specific gastrointestinal signs were present when they were first examined. The clinical signs and their incidence in this study were severe lethargy (100%),

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anorexia (84%), severe dehydration (77%), hypothermia (68%), vomiting (35%), abdominal pain (25%), abdominal mass (23%), diarrhoea (15%), dyspnoea (20%) and ataxia (15%). Unfortunately some of this data only applied to the 32 cats that had the necrotising form of pancreatitis, as records were incomplete for the eight cats with suppurative pancreatitis. These findings reflect earlier studies that found cats with pancreatic disease primarily present with lethargy, depression and anorexia (Owens et al 1975, Garvey & Zawie 1984). These are very non-specific signs and occur with many other diseases in cats. Vomiting, which is considered a major clinical sign of pancreatitis in dogs, was only present in 20% and 33% of cats with acute pancreatitis or pancreatic carcinoma respectively in two other reports (Duffell 1975, Banner et al 1979). More recent reports of acute pancreatitis in cats also fail to identify pathognomonic clinical signs (Simpson et al 1994, Bruner et al 1997, Steiner & Williams 1997).

Chronic pancreatitis is much more common in cats than acute pancreatitis (Williams 1996). Furthermore, it is commonly associated with cholangiohepatitis and inflammatory bowel disease (Weiss et al 1996). The form of pancreatitis found in these cats tends to be predominantly interstitial and the clinical signs referable to pancreatitis are mild. Consequently the major clinical signs are usually those of the concurrent disease.

Diagnosis

The changes reported on abdominal radiographs in acute canine pancreatitis are loss of serosal detail, increased opacity (granularity) in the area of the pancreas, displacement of the duodenum laterally, widening of the angle between the pyloric antrum and the proximal duodenum and ileus manifested as dilated loops of bowel (Williams 1996). However, abdominal radiography is not considered useful in the diagnosis of feline pancreatitis as these features are generally absent (Steiner & Williams 1997).

Pancreatic ultrasonography requires an experienced operator and a high-resolution transducer (Lamb 1989). Abnormalities that can be detected include an enlarged, hypoechoic pancreas, cavitatory lesions, dilated pancreatic duct, biliary duct dilation and the presence of peritoneal fluid (Nyland et al 1983, Lamb 1989). Changes in echotexture and identification of localised fluid can also be found with pancreatic neoplasia, therefore ultrasonography cannot determine the cellular process within the pancreas (Saunders 1991, Simpson & Lamb 1995). It is important to remember that dilation of the common bile duct may be found in other conditions like cholelithiasis (Leveille et al 1996). Although the findings with diffuse pancreatitis may be non-specific, ultrasonography is very sensitive at detecting pancreatic pseudocysts or abscesses (Hines et al 1996, Van Enkevort et al 1999, Swift et al 2000). Ultrasound guided aspiration of cystic lesions and fluid analysis is often required to differentiate between pseudocysts and abscesses (Bradley 1993).

The packed cell volume is usually increased as a result of dehydration, although after fluid therapy anaemia may be apparent (Kitchell et al 1986, Hill & Van Winkle 1993, Williams 1996). Leucocytosis is a common finding in cats with pancreatitis (Williams 1996). The serum glucose concentration is often mildly increased in cats with necrotising pancreatitis (Hill & Van Winkle 1993, Williams 1996). This elevation may be due to stress-related release of catecholamines and cortisol or hyperglucagonaemia. In cats with suppurative pancreatitis hypoglycaemia is more common (Hill & Van Winkle 1993). In contrast, cats with acute necrotising pancreatitis were found to be hyperglycaemic (64%), glycosuric (60%) and ketonuric (20%) (Hill & Van Winkle 1993). These findings probably support the fact that cats with acute pancreatitis may develop diabetes ketoacidosis.

In an experimental model of feline pancreatitis the serum calcium and phosphorous values were significantly decreased (Kitchell et al 1986). It was not determined whether these findings were due to a change in bound calcium, with a parallel decrease in serum albumin, or due to a decrease in ionised calcium. There was no evidence of precipitated calcium deposits in areas of fat necrosis, which has been postulated as a cause of hypocalcaemia in pancreatitis. Calcium was also marginally decreased in 45% of cats with acute pancreatitis in Hill & Van Winkle's review (1993).

Other electrolyte abnormalities present in pancreatitis reflect the degree of hydration and electrolyte loss though vomiting. Prolonged vomiting and anorexia will result in hypokalaemia, especially in cats (Steiner & Williams 1997, Williams 1996). Fifty-six percent of cats with acute pancreatitis were reported to be hypokalaemic, despite the absence of severe gastrointestinal signs (Hill & Van Winkle 1993). However, there are no specific abnormalities in

serum potassium or sodium detected in cases of pancreatitis that cannot be attributed to anorexia or dehydration.

Liver enzyme concentrations are often increased in acute pancreatitis (Williams 1996). Indicators of hepatocellular injury, alanine-aminotransferase (ALT) and aspartoaminotransferase (AST) increase due to hepatic ischaemia or from the direct exposure of hepatocytes to absorbed toxins (Hill & Van Winkle 1993, Williams 1994). Of the 40 cats reviewed by Hill & Van Winkle (1993), ALT, alkaline phosphatase and bilirubin were increased in 68%, 50% and 64%, respectively. A large percentage of the cats with acute necrotising pancreatitis (78%) had fatty changes and/or necrosis of the liver. This finding suggests that hepatic and post-hepatic mechanisms are responsible for the increase in liver enzymes. Many cases of feline pancreatitis are reported in conjunction with concurrent diseases such as hepatic lipidosis, therefore these increases may not be entirely attributable to the pancreatic inflammation (Akol et al 1993). The conclusion that increases in liver enzymes in cats with pancreatitis is more likely to be due to liver disease is supported by the finding that liver enzymes are not significantly different between groups of cats with hepatic lipidosis alone and those with hepatic lipidosis and acute pancreatitis (Akol et al 1993). In addition, severe jaundice due to extra-hepatic bile duct obstruction has been reported in the cat (Simpson et al 1994).

Azotaemia is not a common finding in cats with acute pancreatitis, but when present is usually pre-renal in origin, reflecting dehydration and reduced glomerular filtration (Hill & Van Winkle 1993, Williams 1994). Hypovolaemia, circulating vasoactive substances or plugging of the renal microvasculature by fat deposits or microthrombi may contribute to acute renal failure during pancreatitis (Williams 1994). Hypercholesterolaemia has been reported in 64% of cats with acute pancreatitis (Hill & Van Winkle 1993). This may be due to concurrent diseases such as hepatic lipidosis or endocrinopathies.

Measurement of amylase and lipase concentrations is the cornerstone of diagnosis of pancreatitis in dogs, but elevation of these enzymes is an inaccurate method of diagnosis of pancreatitis in cats (Kitchell et al 1986, Whitney 1993, Parent et al 1995). In experimentally induced pancreatitis in cats, serum amylase actually decreased to 60–80% below baseline values (Kitchell et al 1986). This is a rare finding in humans or dogs, and in these species is often associated with decreased pancreatic mass. The authors postulated that causes for the decrease in serum amylase could be due to decreased release of the enzyme, increased metabolism or the presence of circulating inhibitory substances (Kitchell et al 1986). The serum amylase returned to baseline concentrations 1 month post-operatively in the two surviving cats. Amylase was not increased in any of twelve cats with naturally occurring pancreatitis in one recent study and other reports of cats with pancreatitis also show that amylase concentrations are frequently within laboratory reference ranges (Hill & Van Winkle 1993, Schaer & Holloway 1991, Simpson et al 1994, Parent et al 1995).

In cats, an increase in lipase values is uncommon in both naturally occurring non-pancreatic diseases and with pancreatitis. This finding is in contrast to the significant increases in lipase demonstrated in feline experimental models (Kitchell et al 1986). In one study lipase was within the reference range in six cats with chronic pancreatitis and 17 cats with hepatic or gastrointestinal disease (Parent et al 1995). Again, cats with acute pancreatitis frequently do not have increased lipase values (Schaer & Holloway 1991, Simpson et al 1994, Parent et al 1995). As a consequence a lipase value within the reference range in a cat with clinical signs compatible with pancreatitis should not be used to rule out pancreatitis. Furthermore, lipase and amylase are produced in sites other than the pancreas and are cleared by the kidneys. As such, massively increased lipase and/or amylase in an older cat is more suggestive of poor glomerular filtration than pancreatitis.

Recently a species-specific radioimmunoassay was developed to measure feline trypsin-like immunoreactivity (TLI) (Steiner & Williams 1996). Similar to dogs, low TLI values have been reported in cats with exocrine pancreatic insufficiency and elevated values in cats with decreased glomerular filtration (Steiner & Williams 1996, Steiner & Williams 2000b). High TLI has been demonstrated in cats with naturally occurring pancreatitis, with a maximum value of 540 µg/l (Parent et al 1995, Bruner et al 1997). Gerhardt and others (1999) measured serum TLI in 30 cats with clinical signs of pancreatitis. Pancreatitis was confirmed on exploratory laparotomy by gross (n=11) or microscopic (n=10) changes. A serum TLI greater than 49 µg/l was used to diagnose pancreatitis in 18 of the 30 cats, resulting in a specificity of 86% and sensitivity of 89%. Unfortunately the authors did not obtain

pancreatic biopsies from all cases to confirm disease, neither did they analyse the correlation between serum TLI and the severity of disease in their group of cats.

Swift et al (2000) measured serum TLI in 30 cats with clinical signs consistent with pancreatitis that had histological analysis of pancreatic tissue. The upper limit of reference range for TLI was 89 µg/l and had a sensitivity of 55% and specificity of 56% for diagnosing pancreatitis. There was no significant difference in TLI values between cats with pancreatic inflammation and those with none. The authors concluded that serum TLI values had a poor correlation with the severity of pancreatic inflammation and that the high rate of false negative results may be due a gradual leak of trypsin that was able to be bound by circulating anti-proteases, and thus not be measured by the assay. Although this explanation is possible for those cats with mild disease, it does not explain the low numbers of cats with acute necrotising pancreatitis (80%) that had TLI values within the reference range. Additionally, a large number of cats with hepatic or intestinal disease, with no evidence of pancreatic inflammation or renal disease, had elevated serum TLI concentrations. As a result, the authors felt that mis-diagnosis of pancreatitis in cats could occur if relying solely on serum TLI. The high prevalence of liver disease in the study by Swift et al (2000) could account for the high rate of false positives. Trypsin has been located in extrahepatic peribiliary glands, and therefore hepatic disease could theoretically result in increased TLI in the absence of significant pancreatic inflammation (Terada et al 1993). At this point in time the clinical relevance of feline TLI as a diagnostic test for pancreatitis in cats is unknown, and further studies are warranted.

Exocrine pancreatic insufficiency (EPI) has been reported in cats, and unlike dogs, is most commonly due to end-stage fibrosis from chronic or recurrent pancreatitis (Garvey & Zawie 1984, Steiner & Williams 2000a). Clinical signs of EPI are similar to those in dogs (polyphagia, weight loss, steatorrhoea) and a recent study suggest that serum feline TLI <8 µg/l is consistent with a diagnosis of EPI (Steiner & Williams 2000a).

New diagnostic directions

Due to the poor sensitivity and specificity of current laboratory tests in diagnosing pancreatitis in cats as well as in other species, research is focusing on new methods to definitively diagnose pancreatitis. Trypsinogen activation peptide (TAP) is the cleavage peptide produced when trypsinogen is activated to trypsin (Rinderknecht 1986). Theoretically, TAP should only be detectable in the systemic circulation when there is inappropriate trypsinogen activation within the pancreas instead of the intestinal lumen (Rinderknecht 1986, Hurley et al 1988, Gudgeon et al 1990). TAP is a small oligopeptide with an amino acid sequence Asp-Asp-Asp-Asp-Lys that is common to all vertebrates including cats (De Haan et al 1975, Rinderknecht 1986, Steiner & Williams 1995). Studies have found increased TAP concentrations in plasma, peritoneal fluid and urine from humans and dogs with naturally occurring pancreatitis (Gudgeon et al 1990, Heath et al 1994, Mansfield & Jones 2000). There is a significant correlation between TAP measurements and the presence of necrotising, or severe, pancreatitis in people, whilst they are seldom elevated in mild pancreatitis (Gudgeon et al 1990, Banks et al 1996, Tenner et al 1997, Neoptolemos et al 2000). We have used an enzyme immunoassay (Biotrin, Dublin, Ireland) to measure TAP in healthy cats and cats with pancreatitis. Our initial results show that there is a narrow reference range for plasma TAP (<0.56 nmol/l) in healthy cats, but much more variability in urinary TAP values. This is a similar finding to dogs (Mansfield & Jones 2000). We have measured markedly increased plasma TAP (>16.0 nmol/l) in two cats with necrotising pancreatitis, but have not completed analysis of data from other cats. Initial results suggest that TAP measurement may be an insensitive test for chronic, interstitial pancreatitis in cats.

It has been shown that circulating trypsin-α_1-antiprotease complexes are markedly elevated in people with pancreatitis, and also correlate well with the clinical severity of the disease (Borgstrom & Lasson 1984, Hedstrom et al 1996b). Recently, complexes have been detected in the circulation of healthy people, making the measurement of trypsin complexes less useful as a sole diagnostic test for pancreatitis (Kemppainen et al 1997). Increased circulating tryspin-antiprotease complexes have been reported in dogs with experimental pancreatitis (Williams et al 1996). There are no reports of the measurement of trypsin-α_1-antiproteases in dogs or cats with naturally occurring pancreatitis.

The measurement of carboxypeptidase activation peptide (CAPAP) is also being evaluated in people (Appelros et al 1998). Carboxypeptidase is activated by trypsin, and therefore the

release of CAPAP into the circulation occurs well after the development of pancreatitis. In addition, CAPAP is a larger molecule than TAP, and may be easier to measure (Buchler et al 1998). The use of a urinary test strip to detect trypsinogen-2 has also been investigated in people (Hedstrom et al 1996a). Preliminary research suggests that cationic (type 2) trypsinogen is the main type present in cats (Steiner & Williams 1995). At present these tests are under investigation in people and laboratory animals, and their relevance to the diagnosis of feline pancreatitis is unknown.

Other diagnostic tests assess the severity of pancreatitis by measuring circulating activated proteases or non-specific markers of inflammation. Elevated circulating phospholipase A2 has been found to correlate with the severity of pancreatitis in people, as well as having a strong association with systemic inflammatory response (SIRS) and necrosis of the pancreas (Mayer et al 1998, Hieteranta et al 1999). Increased polymorphonuclear elastase (PMNE) and C-reactive protein concentrations have been reported in people with severe pancreatitis and multi-organ failure (Wilson et al 1989, Dominguez-Munoz et al 1991, Ikei et al 1998). Microalbuminuria is also reported to predict outcome in people with pancreatitis (Shearman et al 1989, Evans & Greaves 1999). Again there have been no studies in cats.

Recent research has focused on the role of cytokines in pancreatitis. Increased interleukin-6 has been shown to be a very sensitive indicator of severe, systemic disease (Leser et al 1991, Ikei et al 1998). The presence of pancreatic necrosis strongly correlates with elevated interleukin-8 concentrations (Rau et al 1997). Furthermore, decreased concentrations of the pro-inflammatory cytokine interleukin-10 (IL-10) have been measured in severe pancreatitis, and the addition of IL-10 to experimental models has alleviated the severity of disease (Van Laethem et al 1995, Chen et al 1999). Circulating α-macroglobulins were within the reference range in one recent study of naturally occurring pancreatitis in dogs (Ruaux & Atwell 1999). Assessment of inflammatory markers in cats with spontaneous pancreatitis has not been reported.

Treatment

Despite increased knowledge about pancreatitis in cats there is a paucity of information in the literature regarding treatment of cats with pancreatitis. The general guidelines include supportive therapy and paying particular attention to fluid and electrolyte requirements (Williams 1996). These guidelines are particularly important when severe disease is present, as hypotension and systemic complications are more likely to develop. Broad spectrum antibiotic therapy should be administered when there is a suspicion of a pancreatic abscess or infection ascending the common pancreatic/bile duct.

It is generally accepted in dogs that no food should be given during episodes of pancreatitis to 'rest' the gastrointestinal tract (Williams 1994). However, vomiting is not a common feature of pancreatitis in cats and fasting may not be of any benefit. Alimentary support via per-cutaneous gastrostomy (PEG) or nasogastric tubes is not contraindicated in the absence of vomiting. In many cats with acute pancreatitis, diseases such as hepatic lipidosis may be present that require nutritional support and fasting should be avoided (Steiner & Williams 2000a).

When concurrent diseases are present they should be treated, even if the treatment appears contraindicated for pancreatitis (Steiner & Williams 2000a). The concurrent diseases are often severe and primarily responsible for the clinical signs present. Diabetes mellitus and diabetes ketoacidosis should be treated aggressively and appropriately. When pancreatitis is present in a diabetic cat stabilisation is more likely to be difficult and closer attention must be paid to electrolyte and fluid balances (Goossens et al 1998). Insulin is required for stabilisation as oral hypoglycaemics are inappropriate if pancreatitis is diagnosed or suspected, and the amount of insulin required is increased during episodes of pancreatitis (Goossens et al 1998). Cats that develop diabetes ketoacidosis as a result of pancreatitis may not be overtly diabetic shortly after recovery from pancreatitis, but generally have insulin resistance and often become diabetic.

It has been shown in people and dogs with experimental pancreatitis that circulating macroglobulins are depleted in severe pancreatitis (Lasson & Ohlsson 1984). Administration of plasma has not been shown to be of benefit in treating severe pancreatitis in dogs, but strong anecdotal evidence suggests that it is helpful (Williams 1996). No studies have been undertaken in cats to determine the value of plasma administration, but extrapolation of observations for dogs would suggest that plasma transfusions may help alleviate systemic complications associated with severe pancreatitis as well as

increase oncotic pressure. Research is being undertaken in human subjects to assess the effectiveness of substances like platelet-activating factor antagonists or nitric oxide to prevent development of complications in acute pancreatitis (Formela et al 1994, Werner et al 1998). Their usefulness in domestic animals, including cats, with acute pancreatitis is unknown.

Local complications may occur in cats with pancreatitis and patients need to be checked for their occurrence. Peritonitis is an uncommon finding in cats with pancreatitis alone, but may occur when liver disease is also present (Akol et al 1993). Pancreatic abscesses and pseudocysts may also develop in cats (Hines et al 1996). Peripancreatic abnormalities are best detected with abdominal ultrasound (Geokas et al 1985, Swift et al 2000). Although many pancreatic pseudocysts may resolve without treatment they can cause necrosis of pancreatic tissue (Bradley 1993). Percutaneous drainage is the treatment of choice in humans (Geokas et al 1985). Mixed success has been reported in the veterinary literature with both open surgical and percutaneous drainage of pancreatic masses (Bellenger et al 1989, Hines et al 1996, Van Enkevort et al 1999). Aspiration of fluid contents via ultrasound guidance is currently recommended to differentiate between abscesses and pseudocysts (Bradley 1993, Van Enkevort et al 1999). The decision whether to perform invasive procedures to drain or remove pancreatic masses should be made on an individual basis, taking into consideration the severity of the illness. Surgical procedures such as cystojejunostomy may also be necessary if the common bile duct is obstructed by a pancreatic or peripancreatic mass.

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