Acute pancreatitis and acute kidney injury in dogs

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ABSTRACT

Acute pancreatitis and acute kidney injury are well-documented comorbidities in human medicine. Dogs that develop acute kidney injury during hospitalization have significantly higher mortality rates than those that do not. The aim of this study was to evaluate the prevalence of acute kidney injury in dogs with acute pancreatitis and the prognostic value of various clinicopathological parameters. Cases of acute pancreatitis presented between January 2012 and June 2016 were identified. The diagnosis of acute pancreatitis was based on two or more of the following clinical signs: abdominal pain, diarrhea, vomiting or anorexia/hyporexia, no other abdominal extra- pancreatic diseases at abdominal ultrasound, and abnormal SNAP cPL test. Diagnosis of acute kidney injury was based on the guidelines of the International Renal Interest Society. Dogs were classified into survivors and non-survivors. Serum creatinine, urea, amylase, total calcium, total cholesterol, C- reactive protein, WBC and band neutrophils were evaluated at admission. Clinical severity index was calculated at admission. Clinical and clinicopathological data were compared between survivors and non-survivors. Sixty-five dogs with acute pancreatitis were assessed. Clinical severity index >6.5 were associated with poor outcome (P=0.0011). Serum urea and creatinine concentrations at admission were significantly lower in survivors than non-survivors (P<0.0001 and P=0.0002, respectively). Acute kidney injury was diagnosed in 17/65 dogs (26.2%) and was associated with poor outcome (P < 0.0001). Oligo-anuria was associated with poor outcome (P=0.0294). Increased clinical severity index and azotemia in dogs with acute pancreatitis were associated with an increased risk of mortality. Acute kidney injury may be a comorbidity of canine acute pancreatitis. The presence of oligo-anuria is associated with poor outcome.

Introduction

Acute pancreatitis (AP) is an acute inflammation of the exocrine pancreas characterized by non-specific clinical signs, which may include anorexia, vomiting, diarrhea and abdominal pain (Mansfield, 2012; Xenoulis, 2015). In the absence of histopathology, clinical history, physical examination, abdominal ultrasound, and canine pancreatic lipase test are currently used to diagnose AP in dogs (Steiner et al., 2008; Mansfield, 2012; Xenoulis, 2015). Acute kidney injury (AKI) is defined as a rapid decline in renal function leading to retention of uremic wastes, modification in fluid status, and electrolyte and acid-base imbalances (Ross, 2011). Diagnosis of AKI is currently based on the evaluation of clinical history, biochemical parameters, especially azotemia, abdominal ultrasound, and urine output (evidence of oliguria or anuria)[1] . AKI in dogs has a poor prognosis, with a mortality rate of approximately 50–56% (Vaden et al., 1997; Thoen and Kerl, 2011). In human medicine, AKI and AP are common comorbidities (Petejova and Martinek, 2013; Zhou et al., 2015). Acute pancreatitis can lead to AKI via hypovolemia, cytokine-induced ischemia, inflammation and oxidative stress (Mansfield, 2012; Petejova and Martinek, 2013). Acute pancreatitis-induced AKI is a well- documented complication in human intensive care units. Dogs that develop AKI during hospitalization have significantly higher mortality rates compared with those that do not (20.5% vs 44.9%; Zhou et al., 2015). To the best of our knowledge, there are no specific clinical studies investigating the association between AP and AKI in dogs. The aims of this retrospective study was to retrospectively evaluate the prevalence of AKI in canine patients with AP and to determine the prognostic value of various clinicopathological parameters.

Materials and methods

Study design, inclusion criteria and study groups

Cases of AP, admitted to the Veterinary Teaching Hospital between January 2012 and June 2016, were identified from the hospital management system. The diagnosis of AP was based on (1) two or more of the following clinical signs: abdominal pain, diarrhea, vomiting or anorexia/hyporexia; (2) the presence of an abdominal ultrasound performed by a radiologist (Xario XG, Toshiba) without other identifiable extra-pancreatic diseases; and (3) abnormal IDEXX SNAP cPL test result. Abdominal ultrasound was considered consistent with AP diagnosis if there were hypoechoic areas within the pancreatic parenchyma, hyperechoic

mesenteric areas surrounding the pancreas, an enlarged pancreas with an irregular profile, and abdominal effusion (Xenoulis, 2015). Dogs without ultrasonographic features consistent with pancreatitis at admission were also included in the study population if they had compatible clinical and clinicopathological features and developed ultrasonographic findings compatible with AP within 3 days from their admission. Dogs with a diagnosis of history of renal diseases or managed with hemodialysis were excluded along with dogs with acute abdomen of non-pancreatic origin and dogs that received drugs known to be nephrotoxic (i.e. nonsteroidal anti- inflammatory drugs, aminoglycosides). The severity of AP was assessed using the clinical severity index (CSI) as described by Mansfield et al. (2008), (see Appendix: Supplementary material). Dogs were screened for systemic inflammatory response syndrome (SIRS) using criteria proposed by Hauptman et al. (1997). A SIRS grading was obtained based on how many criteria were fulfilled; thus the SIRS scores ranged from 2 to 4. Diagnosis of AKI was based on the guidelines of the International Renal Interest Society (IRIS): rapid onset (<1 week) of clinical signs (depression, vomiting, anorexia, weakness, diarrhea), evaluation of hematobiochemical markers compatible with AKI (increase in creatinine!0.3mg/dL or more within 48h), and evidence of oliguria and/or anuria. Acute kidney injury was graded based upon the highest value of serum creatinine observed within 48 h from the admission. Each grade of AKI was further subgraded according to urine production as non-oliguric (>1 mL/kg/h over 6 h; NO) or oligoanuric (<1 mL/kg/h over 6 h; O).[1] Dogs were divided into two groups: survivors and non-survivors. Non- survivors included dogs that died or were euthanased within 7days from admission. Serum creatinine, urea, amylase, total calcium, total cholesterol, C- reactive protein (CRP), WBC and band neutrophils at admission were compared between survivors and non-survivors. Urine was collected and analysed within 12 h of hospital admission. Urine protein/creatinine ratio (UP/UC) > 0.5 was considered pathological proteinuria and was compared between survivors and non-survivors using 2.0 as the threshold value for severe proteinuria (Harley and Langston, 2012).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software). For all continuous parameters, the normality of data distribution was evaluated by means of the D'Agostino-Pearson test. Normally and non-normally distributed continuous parameters are reported as mean ± SD and as median and

range, respectively. An intergroup comparison was performed using a Mann– Whitney U test and a Fisher exact test. ROC curves were created and utilized to optimize decision thresholds to distinguish CSI score groups. Optimal decision thresholds were then evaluated by likelihood ratios. Kaplan–Meier survival curve was performed between CSI score groups. The odds ratio (OR) was calculated. A value of $P < 0.05$ was considered significant. All tests were submitted to an evaluation of post-hoc statistical power using a post-hoc power calculator.[2]

Results

Study population

Of the 101 dogs initially screened for eligibility, 65 were included in this study (Fig. 1). The cohort of dogs included 30 females (46.2%), of which 10 were spayed, and 35 males (53.8%), of which two were neutered. There was a median age of 9.9 years (range 0.7–14.6 years). The most common breeds were German shepherd (n = 4), Rottweiler (n = 3), Beagle (n = 3), Siberian Husky (n = 3), Yorkshire terrier (n = 2), Springer spaniel (n = 2), Labrador retriever (n = 2), Doberman Pinscher (n = 2), Cavalier King Charles spaniel (n=2), Dachshund (n=2); there were 23 other breeds represented in the remaining dogs. There were 17 mixed breed dogs. The overall mortality rate was 27.7% (n = 18/65 dogs); seven dogs were euthanased. None of the dogs were euthanased for financial or non-health related concerns. Four of the seven euthanased dogs developed deterioration of clinical conditions associated with a worsening of azotemia and development of oligo-anuria; two dogs had end stage mast-cell tumor and multicentric lymphoma, respectively, as well as AP, and developed severe neutropenia; one dog had dilated cardiomyopathy and AP. Survivor and non-survivor groups were not statistically different in terms of age and sex.

Clinical severity index

Clinical severity index score obtained from an ROC curve (Fig. 2) was used to divide dogs into two groups: CSI > 6.5 (n = 26) and dogs with CSI < 6.5 (n = 39). Dogs with CSI > 6.5 on admission had a 50% 7-day mortality rate compared with a 12.8% 7-day mortality rate in dogs with CSI < 6.5 ($P = 0.0011$; Fig. 3).

Systemic inflammatory response syndrome

Systemic inflammatory response syndrome was present in 83% of dogs (n = 54/65). Nineteen dogs were included in the group that met two of four SIRS criteria; 20 in the group that met three of four SIRS criteria; and the remaining 15 dogs fullfilled all four SIRS criteria. Systemic inflammatory response syndrome and SIRS grade were not associated with outcome (P = 0.3282 and P = 0.1236, respectively) (Fig. 3).

Biochemical and urinary parameters

Serum concentrations of creatinine, urea, amylase, cholesterol, total calcium, CRP, WBC and band neutrophils in survivors and non-survivors are presented in Table 1. Serum creatinine and urea concentrations were statistically associated with mortality (P=0.0002 and P<0.0001, respectively). Thirty-three urinalyses were available to evaluate proteinuria; seven were excluded due to active sediment. UP/UC > 2 (n = 6) was statistically associated with mortality (P = 0.0181; post-hoc power test 67%;).

AKI

Seventeen of 65 dogs (26.2%) had AKI (AKI group); one, four, seven, two and three dogs were classified as AKI stage I, II, III, IV and V, respectively. The AKI group mortality rate was 70.6% (n = 12/17 dogs). The presence of AKI was statistically associated with increased mortality rate (P<0.0001; post-hoc power test 99.5%; OR 13.37; 95% confidence interval 3.58–49.94). All 17 dogs were subgraded based on urine output – nine dogs (52.9%) in the NO group, and eight dogs (47.1%) in the O group. Five of nine dogs in the NO group survived but none of the eight dogs in the O group survived (P = 0.0294; post-hoc power test 86.4%).

Discussion

In this study, AP was diagnosed by the simultaneous presence of an abnormal SNAP cPL test and clinical and laboratory parameters. In a recent study, SNAP cPL showed a sensitivity of 91.5–94.1% and a specificity of 71.1–77.5%, and was considered as the most rapid diagnostic test for AP in dogs (McCord et al., 2012). Another recent study also demonstrated that decreased renal excretion, during experimental AKI, did not lead to substantial increases in serum pancreas-specific lipase (Hulsebosch et al., 2016).

The sensitivity of the abdominal ultrasound has been reported to be approximately 68% in dogs with severe AP (Hess et al., 1998), but there are currently no reliable data regarding specificity. Thus, dogs with clinical signs of AP, but with negative ultrasound examinations, were also included. Dogs undergoing renal replacement therapies were excluded from the present study, as hemodialysis can influence short-term survival, especially in oliguric dogs. Dogs with AKI that fail to respond to medical therapies are likely to die from complications of uremia, if they are not treated with renal replacement therapy (Ross, 2011). Dogs with a pre-existing history of renal disease were excluded from the study, in order to better evaluate the creatinine elevation associated with AP. However, it is possible that dogs with subclinical chronic kidney disease were inadvertently included in the study. The overall mortality rate in our study was 27.7%. This result is in agreement with previously reported data (23% and 40%; Mansfield et al., 2008; Pápa et al., 2011). However, different degrees and inclusion criteria for AP, unspecified treatment modalities, and different populations, make it difficult to compare our results with previous findings. In line with Mansfield et al. (2008), we found a significant association between CSI score and outcome, confirming that greater CSI was significantly associated with higher risk of mortality in dogs with AP. Systemic inflammatory response syndrome was present in the majority of our population, highlighting that this syndrome is fairly common in the population of dogs with AP seen in our practice. This result is in agreement with the literature on AP, and the simultaneous action of pro-inflammatory cytokines and oxidative stress (Pereda et al., 2006) may be responsible for a progression from local to systemic inflammatory status (Booth et al., 2011). Our results show a significant association between azotemia and increased risk of mortality. In canine AP, azotemia has been reported as a prognostic marker (Mansfield et al., 2008; Pápa et al., 2011). One recent survey demonstrated how azotemia can affect the prognosis in dogs with AP; high serum creatinine and urea were associated with an increased mortality rate (Marchetti et al., 2017). In this study, UP/UC > 2 was associated with mortality. This result agrees with previous literature, in which high levels of UP/ UC were indicative of significant primary renal damage, which could negatively influence prognosis (Cowgill and Langston, 2011). It should be emphasised that this result must be interpreted with caution due to the low post hoc power value (67%). In the present study, 17 dogs had AKI. The AKI group had a higher mortality rate than the overall mortality rate for all dogs. During AP, AKI can occur due to various mechanisms previously described, including events that lead to renal microcirculation damage, which could exacerbate ischemia and

hypovolemia, thus worsening kidney damage (Mansfield, 2012; Petejova and Marti- nek, 2013; Kumar et al., 2015). In our study, approximately half of the dogs with AKI (n = 8) were oliguric. These dogs had a higher mortality than dogs in the NO group. A recent canine study investigating urinary output in naturally-occurring AKI reported that survivors produced significantly more urine over the study period than non-survivors (Brown et al., 2015). Non-oliguric AKI appears to have a better prognosis than oligoanuric AKI, possibly due to different degrees of renal impairment (Brown et al., 2015). In veterinary medicine, there are no published clinical studies on the association between AP and AKI in dogs. Conversely, in human medicine various studies have shown that AKI, besides being one of the most common complications of AP, is associated with poor outcome (Kes et al., 1996; Kumar et al., 2015; Zhou et al., 2015). A recent study also demonstrated that using AKI grading can be helpful in determining prognosis in human patients with AP (Zhou et al., 2015). Our data seem to suggest that AKI, as in human medicine, could significantly influence prognosis. This study has several limitations. In this retrospective work, some dogs may have had comorbidities, which although were not individually analysed, were included in the assessment of CSI. Secondly, we were unable to standardise AP management; however, all the dogs in the present study received similar medical management (fluids, maropitant, ampicillin, metronidazole, omeprazole, and low fat diets). The effects of drugs administered before and during hospitalization on mortality were not consid-ered. In future investigations, it would be useful to monitor changes in serum urea and creatinine, to better understand the role of renal function during canine AP. Necropsy examination was not performed in any of the dogs included in this study and histopathologic confirmation of pancreatic and/or renal disease was not obtained. Finally, it was not possible to demonstrate whether AP was a cause or a consequence of AKI, or if there was a common cause for the two conditions.

Conclusions

Increased CSI, azotemia and oligo-anuria were associated with an increased risk of mortality in dogs with AP. AKI may be a comorbidity of canine AP and associated with increased mortality rate, as well as the presence of oligo-anuria. Early AKI evaluation during AP could possibly provide important prognostic information and suggest useful therapeutic interventions.

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