Role of urinary biomarkers in investigating AKI in dogs

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Researchers at University College Dublin are investigating urinary biomarkers as early markers to detect acute kidney injury (AKI) in dogs in order to prevent more severe and chronic damages commonly associated with AKI

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Acute kidney injury (AKI) is a complex clinical syndrome that can be reversible or can lead to non-reversible kidney damage and sometimes death. Acute kidney injury has been reported in dogs and is associated with increased morbidity and mortality. The International Renal Interest Society (http://www.iris-kidney.com/), a veterinary society promoting standard definition and standard of care recommendations for renal diseases, defines AKI as a continuum of disease with progression over five grades based on the presence of azotaemia. Further investigation of new biomarkers for early recognition is thus very important to better detect AKI and prevent irreversible alteration in a dog's renal function.

BACKGROUND

AKI has been reported to increase morbidity and mortality when it develops in dogs hospitalised in veterinary intensive care units. It was documented in 12 per cent of dogs with naturally occurring abdominal sepsis with only 14 per cent of affected dogs surviving to hospital discharge. Another study reported that AKI developed in 14.7 per cent of all non-azotaemic dogs hospitalised in an ICU setting and that they were less likely to survive.

However, AKI is potentially a reversible syndrome and early recognition is vital for prevention. Tubular changes are the earliest identified on histopathology and proximal tubular proteins such as urinary GGT (uGGT), lipocalin-2 (uNGAL), Cystatin C (uCysC), Clusterin, Kidney Injury Molecule 1 (uKIM-1), Osteopontin (uOPN) and various pro-inflammatory interleukin (IL-6, IL-8 and IL-18) have been shown to increase in the urine of humans with AKI, and to correlate with histopathological changes in humans, rats and dogs. Urinary biomarkers have also been shown to detect subclinical changes in renal function (corresponding to stage 1 AKI).

As early markers of AKI, their use is more and more popular in human medicine. However, limited published data is currently available. Urinary biomarkers correlated with early tubular damage in a genetic model of degenerative renal disease in dogs. Urinary retinol binding protein (uRBP) was strongly correlated with tubule-interstitial lesions and disease progression, making it a good candidate biomarker for early-stage AKI. Its value was subsequently confirmed in naturally occurring canine chronic kidney disease.

Other biomarkers of tubular injury such as uGGT, uKIM-1, uRBP and uNGAL have been investigated in dogs with naturally occurring AKI, including those with underlying infectious aetiologies such as babesiosis, parvoviral infection or leishmaniasis. Similarly, uCystC was evaluated in both naturally occurring renal disease as well as a haemorrhagic shock model. Similar haemorrhagic shock models have validated the use of urinary interleukin 8 (uIL-8), monocyte chemoattractant protein 1 (uMCP-1) and clusterin (uCLU) along with uCystC, uNGAL and uKIM-1. Researchers at the UCD School of Veterinary Medicine believe that further investigations are required to understand the performance and potential value of these biomarkers in a clinical setting.

Various causes of AKI have been reported in both humans and veterinary species. Contrast-induced nephrotoxicity (CIN) manifests as an abrupt decline in renal function within 24 to 72 hours of contrast administration in the absence of an alternative cause. In humans, the frequency of CIN following administration of iodinated intravenous contrast products varies between two and 14.7 per cent. In one study, two per cent of patients with CIN died within 45 days. Another study reported the need for dialysis in 6.5 per cent of these patients. Finally, CIN is poorly characterised in veterinary medicine. Reports of CIN in the veterinary literature is scarce but it is reported in 0-7.6 per cent of cases in dogs undergoing CT with intravenous contrast administration. There is no data available on urinary biomarkers for AKI in dogs undergoing contrast-enhanced CT.

STUDY DESIGN

The current proposed pilot study is the first to investigate CIN prospectively and to use urinary biomarkers to identify early-stage AKI in dogs. The investigators expect to determine the prevalence of suspected CIN based upon changes in urinary biomarkers but also to compare the performance of various urinary biomarkers.

Free catch urine from dogs undergoing contrast enhanced CT at the university college Dublin is collected prior to and after the imaging study is performed. Control groups including dogs having non-contrast CT, healthy dogs and dogs presented to the UCD Veterinary Hospital with AKI are also being enrolled. Statistical analysis will aim to look at changes in urinary biomarkers in patients undergoing CT and the effects of contrast administration on these urinary biomarkers. Correlation between the various urinary biomarkers will also be investigated.

References available on request.