



Changes in the serum urea: Creatinine ratio in dogs with babesiosis, haemolytic anaemia, and experimental haemoglobinaemia

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ABSTRACT

The purpose of this study was to determine serum urea and creatinine concentrations, the derived urea : creatinine (UC) ratios, haemoglobin concentrations and glomerular filtration rates (GFR) in dogs with haemolytic anaemia and those with experimentally induced anaemia and/or haemoglobinaemia. There were 25 dogs with babesiosis (group 1), 13 control animals (group 2), six dogs with induced haemoglobinaemia and anaemia (group 3), six with induced haemoglobinaemia (group 4), and 14 with immune-mediated haemolytic anaemia (IMHA) (group 5).

The median serum urea concentration was 11.18 mmol/L (group 1), 4.3 mmol/L (group 2), 4.3 mmol/L (group 3), 4.35 mmol/L (group 4), and 8.5 mmol/L (group 5). Median serum creatinine was 67 μ mol/L (group 1), 75 μ mol/L (group 2), 78.5 μ mol/L (group 3), 84 μ mol/L (group 4), and 82 μ mol/L (group 5). Median serum haemoglobin was 1.3 g/L (group 1), 0.8 g/L (group 2), 9 g/L (group 3), 3 g/L (group 4), and 1.3 g/L (group 5). The median UC ratio was 41.35 (group 1), 15.36 (group 2), 14.18 (group 3), 13.6 (group 4), and 14.15 (group 5). GFR was normal in all five groups. Serum urea concentration and the UC ratio were significantly greater in dogs with babesiosis than in those with IMHA, experimentally induced anaemia and/or haemoglobinaemia.

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Introduction

The normal serum urea : creatinine (UC) ratio in the dog is reported to be in the range 10–15 (Médaille et al., 2004). In humans, a serum UC ratio ≥ 20 in an azotaemic patient is indicative of pre-renal azotaemia, whereas a ratio < 20 is indicative of intrinsic renal disease (Brady and Brenner, 1994). This implies that serum urea is more likely to increase due to pre-renal factors than serum creatinine, whereas both parameters are equally likely to rise in renal disease.

In a retrospective study of 4799 canine urea and creatinine data sets, 27.5% of dogs showed an elevated serum UC ratio (Médaille et al., 2004). The study concluded that although changes in creatinine associated with breed and muscle mass were significant, they did not account for all of the changes and it was speculated that pre-renal influences were present. A marked increase in serum UC ratio has been linked to acute renal azotaemia, pre-renal azotaemia, or a disrupted urinary tract with urine leakage (Jacobson and Lobetti, 1996).

Azotaemia is common in canine babesiosis (Reyers et al., 1998). In a retrospective study of 400 *Babesia canis* cases, the median serum urea concentration was approximately double the normal lab-

oratory range, whilst the median serum creatinine concentration fell within the normal laboratory range (De Scally et al., 2004).

Possible causes of an elevated serum urea concentration encountered in haemolytic disease include artefactually elevated urea, gastric ulceration, dehydration, hypotensive shock, cardiac disease, rhabdomyolysis, and hyperureaogenesis from substrate loading (Finco, 1997; Freeman et al., 1994; Jacobson and Lobetti, 1996; Lyman, 1986; Médaille et al., 2004; Michel et al., 1997; Olde Damink et al., 1999; Prause and Grauer, 1998; Reyers, 1992; Sklar et al., 1996). It is possible that in haemolytic disease an elevated serum UC ratio may also be caused by haemolysis, interference with light transmission causing a falsely elevated urea, by pre-renal azotaemia, or by serum substances interfering with serum creatinine analysis (Bauer, 1980; Blank et al., 1985; Dorner et al., 1981; Franzini et al., 1991; Jacobs et al., 1991; Soldin et al., 1978; Weber and van Zanten, 1991). This is consistent with the increased serum urea and UC ratio reported in cases of intestinal haemorrhage, acute tubular necrosis, excessive protein loading or increased protein catabolism, where hyperureaogenesis is common (Prause and Grauer, 1998; Sklar et al., 1996).

It has been suggested that ammonia loading may occur with haemolysis, blood transfusions, and gastro-intestinal haemorrhage (Reyers, 1992). This could lead to a non-renal related elevation in serum urea concentrations via hyperureaogenesis and could cause the increased serum UC ratio apparent in canine babesiosis (De

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Sally et al., 2004). Most non-creatinine serum chromagens may cause a false increase in creatinine, which would decrease the UC ratio (Braun et al., 2003). In contrast, bilirubin could cause a negative interference with creatinine measurement that would increase the UC ratio (Bowers and Wong, 1980).

A study by De Sally et al. (2006) confirmed that serum urea concentrations are disproportionately increased relative to serum creatinine in canine babesiosis. The study showed that median serum urea was elevated, median serum creatinine was within normal reference ranges, and median serum UC ratio was significantly elevated. The authors hypothesized that some of the dogs with high serum urea and normal or low serum creatinine concentrations may have had renal azotaemia. They suggested that serum creatinine may have been low due to interference with laboratory measurements by the blood pigments encountered in canine babesiosis. In haemolytic disease, haemoglobin can interfere with the biochemical analysis of serum creatinine concentrations when the kinetic Jaffé alkaline picrate or the indirect enzymatic colorimetric test is used (Bauer, 1980; Jacobs et al., 1991; Soldin et al., 1978; Weber and van Zanten, 1991).

The hypothesis of the present study was that an elevated UC ratio in canine babesiosis is not due to renal disease, interference of haemoglobin and/or bilirubin on creatinine measurement, and/or hypovolaemia. The aim therefore was to determine serum urea, creatinine and haemoglobin concentrations, the UC ratio, and glomerular filtration rate (GFR) in dogs with haemolytic anaemia and in those with experimentally induced haemoglobinaemia and/or anaemia.

Materials and methods

Study design

The study was approved by the Ethics and Research Committees of the Faculty of Veterinary Science, University of Pretoria and written consent by the dogs' owners was obtained.

Five groups of dogs were used: 25 had severe babesiosis (group 1), 13 were controls (group 2), six had induced haemoglobinaemia and anaemia (group 3), there were six with induced haemoglobinaemia (group 4), and 14 with primary immune-mediated haemolytic anaemia (IMHA) (group 5).

Group 1 dogs with natural infection were diagnosed using a thin capillary blood smear stained with Cams Quick stain (CA Milsch), plus severe anaemia (haematocrit <15%) and no clinical or biochemical signs of complicated disease. Group 2 comprised healthy dogs that had been presented for routine ovariohysterectomy or castration, showed no abnormalities on clinical examination, were negative for *B. canis* on peripheral blood smear examination, and had a normal haematocrit.

Data from a previous publication (Lobetti et al., 1996) were used for groups 3 and 4. Briefly, group 3 were experimental dogs that over a 4-day period had been bled to a haematocrit of 12% and had a total of 300 g homologous haemoglobin infused together with volume replacement to maintain normovolaemia. Group 4 were experimental dogs that over a 4-day period had a total of 300 g homologous haemoglobin infused. Group 5 had all been diagnosed with primary IMHA by ruling out secondary causes using survey thoracic radiographs, abdominal ultrasonography, blood smear and PCR assays for parasites, and serum biochemistry.

Data collection

Each dog had one blood sample collected from the jugular vein into a 3 mL serum vacuum tube. Samples from groups 1 and 5 were collected prior to any treatment being administered. Samples from groups 3 and 4 were collected at the end of day 4. Serum urea, creatinine, and serum haemoglobin were measured. Urea and creatinine were converted to mg/dL for the calculation of serum UC ratio in order to ensure equivalent units. GFR was determined by serum cystatin-C concentration in groups 1, 2, and 5 and by the exogenous creatinine clearance in groups 3 and 4.

Serum urea concentrations were measured using the Technicon method (Tiffany et al., 1972), which is a modification of the enzymatic method of Talke and Schubert for the RA-1000 analyzer (Bayer) with a normal range of 4–9 mmol/L. Serum creatinine concentrations were measured using the Technicon method (Rossignol et al., 1984), which is a kinetic modification of the Jaffé alkaline picrate reaction for the RA-1000 analyzer with a normal range of 100–140 µmol/L. Serum cystatin-C concentrations were measured using the particle-enhanced turbidimetric immunoassay (Cystatin-C concentration Diagnostech, Honeydew Dako Cytomation, Cystatin C PET

kit), designed for the determination of human cystatin-C. Normal values were set at <1.7 mg/L according to the control group and the findings of Wehner et al. (2002). The exogenous creatinine clearance was performed as previously reported (Lobetti et al., 1996).

Serum haemoglobin concentration was measured using an adaptation of the Drabkin's cyanmethaemoglobin method (Bauer, 1980) for the Bayer-Technicon RA-XT (Bayer). Samples were considered to have significantly elevated serum haemoglobin if the measured concentration was >1.6 g/L.

Data analysis

Data were tabulated in an Excel spreadsheet and statistical analysis was performed with the aid of a statistical software package (NCSS). The Kruskal–Wallis one-way analysis of variance on ranks was used to test for statistical differences between groups. Correlations between the various parameters were assessed using the Spearman-rank correlation coefficient. The level of significance was set at $P < 0.05$.

Results

Results of the serum urea, creatinine, haemoglobin, and UC ratio are summarized in Table 1. Dogs in group 1 showed an elevated median serum urea (11.18 mmol/L), whereas dogs in groups 2–4 had a median serum urea that was at the lower end of normal: 4.3 mmol/L (group 2), 4.3 mmol/L (group 3), and 4.35 mmol/L (group 4). Group 5 had a median serum urea of 8.5 mmol/L. There was a statistically significant difference ($P < 0.01$) between group 1 and the other groups.

The median serum creatinine value was 67 µmol/L in group 1, 75 µmol/L in group 2, 78.5 µmol/L in group 3, 84 µmol/L in group 4, and 82 µmol/L in group 5, with no statistically significance between the five groups, although there was a trend towards lower creatinine values in group 1. There was, however, no correlation with serum bilirubin which excludes a negative interference with creatinine measurements that could falsely elevate the UC ratio.

Median serum haemoglobin concentrations were 1.3 g/L (group 1), 0.8 g/L (group 2), 9 g/L (group 3), 3 g/L (group 4), and 1.3 g/L (group 5). The dogs that had haemoglobin infused showed the highest values. There was a statistically significant difference ($P < 0.01$) between groups 3 and 4 and the other groups. An elevated UC ratio was only evident in group 1 with a median value of 41.35. The UC ratios were 15.36 in group 2, 14.18 in group 3,

Table 1

Serum urea, creatinine, haemoglobin concentrations, and urea : creatinine (UC) ratios in dogs with severe babesiosis (group 1; $n = 25$), control dogs (group 2; $n = 13$), dogs with induced haemoglobinaemia and anaemia (group 3; $n = 6$), dogs with induced haemoglobinaemia (group 4; $n = 6$), and dogs with primary immune-mediated haemolytic anaemia (group 5; $n = 14$).

Parameter	Group	Mean	Median	SD	Range
Urea (mmol/L)	1	12.82	11.18	6.67	3.9–32.8
	2	5.08	4.3	1.89	3–8.9
	3	4.27	4.3	0.98	2.7–5.6
	4	4.58	4.35	1.05	3.3–6.3
	5	9.44	8.5	1.17	3.4–20.5
Creatinine (µmol/L)	1	72.08	67	24.64	22–119
	2	78.69	75	16.64	56–114
	3	77.33	78.5	7.58	66–88
	4	85.5	84	11.34	71–101
	5	90	82	9.11	46–169
Haemoglobin (g/L)	1	1.72	1.3	1.06	0.7–5.1
	2	0.88	0.8	0.48	0–1.6
	3	8	9	4.9	0–12
	4	3	3	3.29	0–6
	5	1.89	1.3	1.28	0.9–5.1
UC ratio	1	46.32	41.35	21.67	17.27–94.86
	2	15.91	15.36	4.15	11.17–25.04
	3	13.61	14.18	2.63	10.13–17.12
	4	13.07	13.6	1.99	10.08–15.45
	5	14.20	14.15	1.75	5.88–32.6

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