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Case Study

A Case of Acute Renal Failure Following Ethylene Glycol Intoxication in a Dog

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ABSTRACT

The manuscript describes a clinical case of severe oligoanuric acute renal failure in a young dog following ethylene glycol intoxication. Significant deviations were established in urinary renal markers and blood biochemical parameters: severe azotemia, hypocalcaemia, hyperphosphataemia, hyperkalaemia and metabolic acidosis. The ultrasound renal findings demonstrated increased renal cortex echogenicity the typical for ethylene glycol intoxication, with a characteristic halo sign around the medulla. Electrocardiography showed a progressive decrease in amplitudes of P and R peaks, increased sharp edged repolarisation T wave. The performed symptomatic therapy did not lead to favourable outcome due to delayed intervention by the owner and non-administered antidotal therapy. The histopathological finding was consisted in degeneration, necrosis, desquamation of kidney epithelial cells, dilated tubules and multiple calcium oxalate deposits. The described changes, in our opinion, are relevant and could be used for diagnostics of the studied pathology.

Key Words: Acute renal failure, ethylene glycol, intoxication, glomerular marker, dogs

ÖZET

BİR KÖPEKTE ETİLEN GLİKOL İNTOKSİKASYONU ARDINDAN GELİŞEN AKUT RENAL YETMEZLİK VAKASI

Bu metin genç bir köpekte etilen glikol intoksikasyonu ardından gelişen şiddetli oligoanürik renal yetmezlik sonucu oluşan klinik vakayı tanımlamaktadır. Üriner renal markerlarda ve kan biyokimyasal parametrelerinde önemli sapmalar belirlenmiştir: şiddetli azotemi, hipokalsemi, hiperfosfatemi, hiperkalemi ve metabolik asidoz. Böbrekteki ultrason bulguları, etilen glikol intoksikasyonunda tipik olarak görülen renal korteks ekojenitesinde artış ile birlikte medulla çevresinde karakteristik hale işaretini ortaya koymuştur. Elektrokardiyografi sonucunda, P ve R piklerinin amplitüdlerinde progresif azalma, T dalgasının tepe noktasının repolarizasyonunda artış meydana geldiği görülmüştür. Uygulanan semptomatik tedavi, hayvan sahibinin gecikmiş müdahalesi ve antidot terapsinin ilaç verilmeden gerçekleştirilmesi yüzünden olumlu sonuca ulaşamamıştır. Görülen histopatolojik bulgular; böbrek epitel hücrelerinin dejenerasyon, nekroz ve deskuamasyonu, tubul dilatasyonu, çoklu kalsiyum okzalat birikintilerinden meydana gelmektedir. Bizce, tarif edilen değişiklikler, çalışılan patolojik durumla ilgilidir ve diagnostik açıdan kullanılabilir.

Anahtar Kelimeler: Akut renal yetersizlik, etilen glikol, intoksikasyon (zehirlenme), glomeruler marker, köpekler

Introduction

Ethylene glycol is a polyvalent alcohol with a sweet taste, high boiling point (198^{o}C) and a low molecular weight (62 g/mol). It is widely applied as a main ingredient of antifreeze liquids in automobile cooling systems. Ethylene glycol is a commonly encountered etiological factor causing acute renal failure in dogs and cats (Connally et al., 2010; Goicoa et al., 2003; Grauer and Thrall, 1982). In some regions of the world, e.g. the Republic of South Africa, only sporadic cases of such intoxications are explicably reported (Keller and Goddard, 2005). The same is the situation in the Republic of Bulgaria, where only two cases of ethylene glycol intoxications in dogs are referred to the Trakia University Small Animal Clinics over a decade (Hristov et al., 2005).

The intoxication is commonly seen in dogs licking antifreeze, even if tap water is available because of flavour taste. The usual cause is the improper storage of the substance and less frequency, an act of malice (Dircks et al., 2007).

Acute ethylene glycol poisoning is serious and with a fatal outcome in more than 88% of cases (Hristov et al., 2005). Rowland (1987) reported that mortality rates in cats are markedly higher, from 96 to 100 %. When comparing the lethal dose, for cats 1.4 ml/kg, the dogs are more resistant, 4.4-6.6 ml/kg (Grauer and Thrall, 1982). The injuries are mainly on the renal parenchyma, with development of acute renal failure. Cerebral damage might also occurred from the narcotic effect of the noxious substance, its metabolites or endogenous toxic products at a later stage. The liver could also be affected, with development of severe toxic hepatitis (Goicoa et al., 2003).

The intoxication could be also chronic, in some rare cases. Choi et al. (2007) described a case of chronic ethylene glycol intoxication in a young dog with secondary renal hyperparathyroidism and jaw bones fibrous osteodystrophy. The described clinical, paraclinical and post-mortem changes in this work are attributed to the reno-metabolic stage of ethylene glycol intoxication. In our belief, the presented clinical case adds to the clinical experience on acute renal failure due to ethylene glycol intoxication in dogs and cats.

Case

History

A mixed breed female dog, 11-month-old, weighing 19 kg was referred to the Small Animal Clinic of the Faculty of Veterinary Medicine, Trakia University, Stara Zagora in April 2012. The dog was privately owned and housed in the yard of an enterprise performing technical and repair activities. Two days ago (50 h) the owner noticed that the dog ingested willingly liquid resembling antifreeze. The dog vomited 30-40 min after the episode and since then, refused to eat. Prior to the referral, no treatment has been applied.

Clinical data

The body size was medium, with relatively good constitution. The dog was obviously reluctant to move, became rapidly exhausted and often lied down. The skin elasticity was reduced (10% dehydration), with mild enophthalmos. The conjunctivae were pale, and capillary refill time was within 2-3 s. The physical examination revealed rectal body temperature 39.7 ^{o}C; heart rate – 136 min $^{-1}$; respiratory rate – 32 min $^{-1}$. Heart auscultation yielded clear and pure sounds. The respiratory movements were strong, symmetric, of the costoabdominal type. Lung auscultation did not reveal any pathological sounds. The abdomen was not protruded, painful when palpated and with abdominal guarding. The faeces were diarrhoeic, yellow-reddish in colour, with unpleasant odour and mixed with significant amount of mucus. The urinary system examination revealed rare urination of scanty cloudy, dark yellow-greenish urine (oliguria). The palpation of the renal area was very painful.

Diagnostics

Blood was sampled for analysis of complete blood count (CBC), biochemistry profile and acid-base status (ABS). The results were indicative of a severe renal damage, which

additionally required a complete urinalysis, abdominal ultrasound and electrocardiography.

The CBC revealed a substantial leukocytosis with total white blood cell counts of 38 x 10^9/L (Table 1, day 0). Red blood cell parameters (haemoglobin Hb, erythrocytes Er and haematocrit Hc) were in the lower reference range for the species. Blood biochemical analysis showed a mild hypocalcaemia, moderate hyperphosphataemia and increased serum potassium levels (Table 2, day 0). Considerable deviations were also observed in blood nitrogen bodies (creatinine and urea), which were higher than a few times more normal. Slight changes have occurred in blood glucose and alkaline phosphatase levels. Blood ABS parameters exhibited a moderate metabolic acidosis with blood pH of 7.21. Along with that, actual bicarbonates (HCO_3), actual base excess (ABE) and partial carbon dioxide pressure (PCO_2) were reduced (Table 2, day 0).

Table 1. Blood haematological parameters in the dog with ethylene glycol intoxication.

Tablo 1. Etilen glikol ile zehirlenen köpeğin kan hematolojik parametreleri

Parameter	Value			Ref. Range
	Day 0	Day 5	Day 10	
Haemoglobin g/L	127	121	105	120-180
Erythrocytes x 10^{12}/L	5.63	5.50	4.77	5.5-8.5
Haematocrit %	36.0	34.8	30.3	37-55
Leukocytes x 10^9/L	38.0	18.1	20.3	6-17
(MCV) fl	64.0	63.4	63.6	60-77
Thrombocytes x 10^9/L	154	108	117	160-430

Reference range – Merck veterinary manual; Hematologic Reference Ranges, NJ USA. 2011

Significant alterations were observed in urinalysis results (Table 3): high extent of proteinuria, albuminuria, detection of C-reactive protein in urine (uCRP/Cr – 2.040 mg/g), glucosuria and haematuria, and sediment findings consisted in crystaluria (calcium oxalate crystals), plenty of erythrocytes, leukocytes, renal epithelial cells and epithelial cylinders.

Ultrasonographically, the kidneys were enlarged, with increased cortical echogenicity, and enhanced corticomedullary distinction (Figure 1).

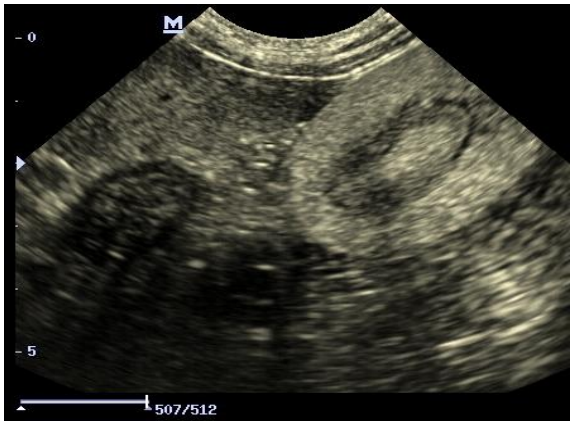

Figure 1. Transverse view of the right kidney in the dog with ethylene glycol intoxication.

Resim 1. Etilen glikol ile zehirlenen köpeğin sağ böbreğinin transversal görüntüsü

ECG findings consisted in progressive decline in P and R peaks' amplitudes, increased and sharp-edged repolarisation T wave.

The analysis of all haematological, blood biochemical, urine, ECG and ultrasound parameters was highly indicative about the reno-metabolic stage of ethylene glycol intoxication. The dog was hospitalized and the treatment included furosemide (4 mg/kg, i.v. at 8 h intervals), Dopamine HCl (3 micro-grams/kg/min), Sodium chloride 0.45% solution, Sodium Bicarbonate 8.4% solution (1 mmol/kg), Calcium gluconate 10% solution (1 mL/kg), Metoclopramide (1 mg/kg/day, i.v.) Famotidine (1 mg/kg/day, i.v.), Vitamin B_1 (100 mg/i.v.) and Synulox (8.75 mg/kg/day, s.c., Pfizer, UK) as the diuresis and fluid and electrolyte balance was monitored. The clinical status was monitored on a daily basis, the

changes consisted in permanent hypothermia, bradycardia and oligopnea. Despite the initiated therapy, the general condition became progressively worsened due to aggravation of uremia (lethargy, arrhexia, vomiting and oliguria). Five days after the beginning of the treatment, blood analysis was repeated. The results showed a tendency for normalisation of leukocyte counts and a negative trend to reduction in red blood indices (Hb, Er and Hc) (Table 1, day 5). The most consistent deviations were established in biochemical parameters. A severe azotaemia was present, with serum creatinine concentrations attaining 1419 μmol/L, i.e. three times the critical value (Table 2, day 5). A similar change was observed in urea concentrations – 62.5 mmol/L. Worsening hypocalcaemia, hyperphosphataemia and hyperkalemia were registered. Despite the progressive character of the reno-metabolic stage, the therapy was not discontinued and the aforementioned parameters were reevaluated on the 10th day of the treatment. The blood azotaemia was extreme with 2173 μmol/L serum creatinine and 68.1 mmol/L urea (Table 2, day 10). A similar tendency was established for serum potassium – a progressing hyperkalemia. The control ultrasound of kidneys showed enlarged size, specific hyperechoic shadows mainly in the cortex, and appearance of new hyperechoic areas in the medulla. A small amount of free abdominal fluid also can be seen (Figure 2).

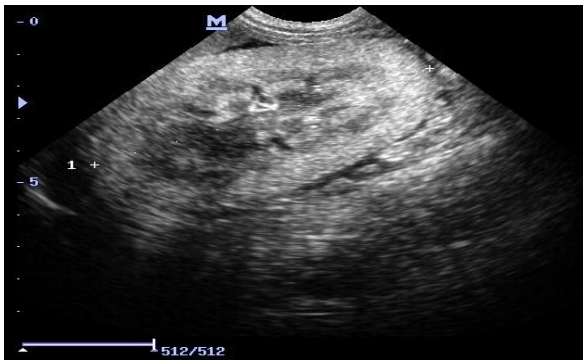

Figure 2. Longitudinal view of the right kidney in the dog with ethylene glycol intoxication.

Resim 2. Etilen glikol ile zehirlenen köpeğin sağ böbreğinin uzunlamasına (longitudinal) görüntüsü

Table 2. Blood biochemical parameters in the dog with ethylene glycol intoxication.

Tablo 2. Etilen glikol ile zehirlenen köpeğin kan biyokimyasal parametreleri

Parameter	Value			Ref. Range
	Day 0	Day 5	Day 10	
Creatinineμmol/L	695	1419	2173	44-138
Urea mmol/L	33.7	62.5	68.1	3.1-9.2
Total protein g/L	56.1	51.3		55-75
Albumin g/L	28.7	27.1		26-40
Blood glucose mmol/L	7.8	5.11		3.4-6.0
ASAT U/L	29	43	44	8.9-49
ALAT U/L	33	40	49	8.2-57
Alk.Phosph. U/L	232	356		10.6-101
Calcium mmol/L	2.1	1.9		2.2-3.0
Phosphate mmol/L	3.27	4.15		1.0-2.0
Sodium mmol/L	141	145		140-154
Chlorides mmol/L	106	113		102-117
Potassium mmol/L	5.7	6.1	6.8	3.8-5.6
pH	7.21			7.31-7.42
HCO_3 act. mmol/L	11			20-29
ABE mmol/L	–14.7			0 - (– 4)
TCO_2 mmol/L	11.9			18-25
$PaCO_2$ mmHg	30			32-49

Reference range - Merck veterinary manual; Biochemical Reference Ranges, NJ USA. 2011

The dog was euthanised due to the extremely poor prognosis and the impossibility for correction of acquired glomerular and tubular damage. After the euthanasia, necropsy was performed and specimens for histopathological examination were collected.

Table 3. Urinalysis results in the dog with ethylene glycol intoxication.

Tablo 3. Etilen glikol ile zehirlenen köpeğin idrar analiz sonuçları.

Parameter	Value
pH	6.5
Protein	+ + +
Glucose	+/-
uCRP/Cr (mg/g)	2.040
Specific gravity	1.035
uAlb (g/L)	2
uAlb/Cr	6387.57
UPC	15.97

The gross inspection of kidneys revealed that they were enlarged and of a cloudy greyish colour. The capsule was easily removed, and the boundary between cortex and medulla was clearly demarcated. The cortex was spattered with grey-yellowish bands and among them, with grey-whitish granular structures, barely visible to the naked eye (Figure 3).

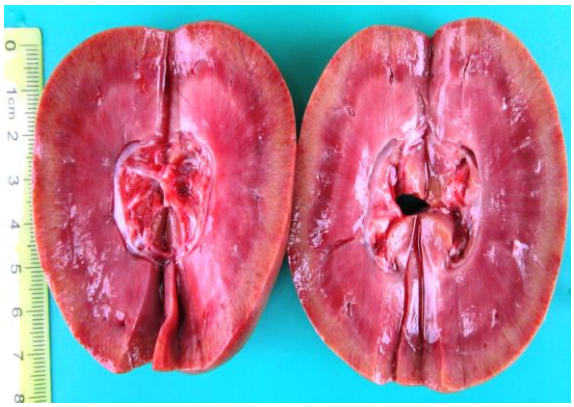

Figure 3. Gross anatomy findings in the kidneys of the dog with ethylene glycol intoxication.

Resim 3. Etilen glikol ile zehirlenen köpeğin böbreklerinin makro anatomik bulguları

In microscopy, multiple areas of epithelial cells of proximal and distal tubules of the renal cortex, vacuolar degeneration was present. The epithelium of the other tubules was desquamated, with lysed nuclei, and completely necrotic in many areas, deposited intraluminally as amorphous granular masses. The same degenerative and necrotic changes were also observed although at a lesser extent, in the renal medulla.

Into the lumens of proximal and distal tubules of the cortex and less frequently in the medulla, there were multifocal depositions of calcium oxalate crystals. Many of affected tubules were visualised in close proximity to the inner side of the basal membrane, replacing the dead epithelial cells. Calcium oxalate crystals were not stained with haematoxylin/eosin but they are visible and can be described (Figure 4). Using Dahl's stain, they were stained in red-orange on the background of the pale green renal tissue (Figure 5).

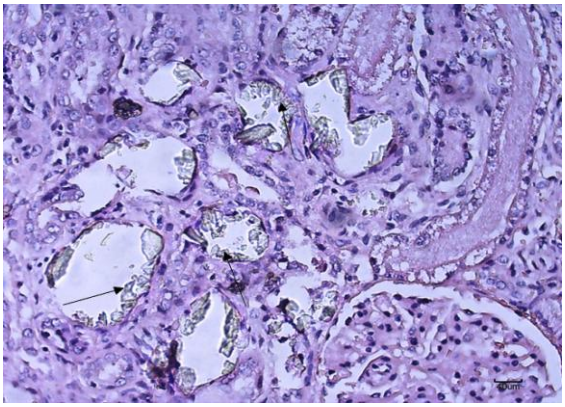

Figure 4. Dilated renal tubules with calcium oxalate crystals (arrow). H/E staining.

Resim 4. Kalsiyum okzalat kristalleri (ok ile gösterilen) ile genişlemiş renal tübüller. H/E boyama.

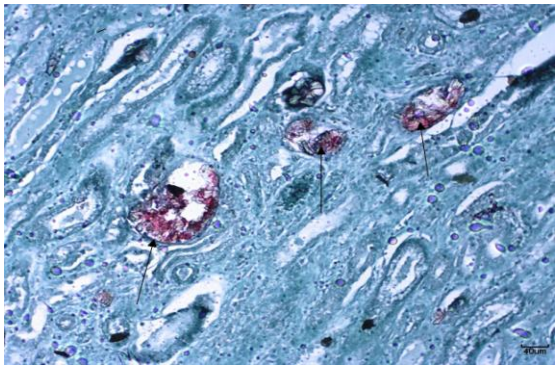

Figure 5. Impaired renal structure with multiple calcium oxalate crystals (arrow). Dahl's staining.

Resim 5. Çoklu kalsiyum okzalat kristalleri ile bozulmuş renal yapı (ok ile gösterilmiş). Dahl boyama.

Discussion

After oral intake, ethylene glycol is absorbed very rapidly in the blood, where under the action of alcohol dehydrogenase and partly of catalase, it is converted into highly toxic metabolites: glycolic acid, glyoxylic acid, oxalic acid and formic acid (Grauer et al., 1984; Hristov et al., 2005). During the first 24 hours (general toxic stage), a gastrointestinal syndrome is manifested, resulting from local irritation effects as well as neurological syndrome due to dystrophic changes of nerve cells induced by glycolic compounds. Renal damage is proper for the second stage of ethylene glycol poisoning. It occurs during the next 24 hours after the intake and is caused by metabolic products inducing dystrophy of the cells of nephron tubular apparatus. A main role in this process caused by oxalic acid and its salts, is known to provoke tubulopathy (Hristov et al., 2005). The researchers also provide evidence for the direct toxic effect of metabolites (glycoaldehyde, glyoxylic and oxalic acid), also causing glomerulopathy. The significant deviations in uAlb/Cr and uCRP/Cr ratios found in this case support the aforementioned. The presence of uCRP means that glomerular barrier is damaged enough to allow filtration of high molecular weight proteins. This finding can be explained with increasing the uCRP/Cr in the course of ethylene glycol intoxication leading to inflammatory response which results in increasing of the plasma concentrations and subsequent pass of CRP through the damaged glomerular barrier (Smets et al., 2010).

In this clinical report, the ethylene glycol intoxication was in a renal metabolic stage. The clinical signs of acute renal failure, accompanied by severe oligo-anuria, azotaemia, proteinuria and crystaluria are due to complex nephropathy (glomerulo- and tubulopathy) induced by toxic ethylene glycol metabolites. The observed gastrointestinal complications – vomiting, anorexia and diarrhoea are due to the direct effect of uremic toxins on vomiting chemoreceptors in the cerebral cortex and to uremic gastroenteritis (Vanhoider, 1998). The uremic gastropathy is attributed by authors to high gastrin concentrations, inducing hydrochloric acid secretion by irritation of gastric mucous receptors.

The established metabolic acidosis (lower values of pH, HCO_3, ABE and PCO_2) results from the limited capacity of damaged kidneys to excrete hydrogen ions. It is also consequent to disturbed ammoniagenesis, the reduced filtration rate of phosphate and sulfate compounds and the loss of bicarbonates (Kimmel, 1998). The registered signs of anorexia, nausea, lethargy and muscular weakness were most probably due to metabolic acidosis (Lulich et al., 1992).

The observed specific ultrasonographic findings were due to accumulation of multiple calcium oxalate crystals, particularly in the cortex and the corticomedullary junction (Civelek et al., 2006). The crystals deposited in the renal cortex increase considerably its echogenicity, forming a specific "frame" surrounding the medulla (Mantis and Lamb, 2000). The observed ECG changes result from disturbances in the repolarisation of heart ventricles consequently to potassium disequilibrium and development of hyperkalemia (Martin, 2001).

The histopathological findings consisting in degeneration, necrosis, desquamation of renal epithelial cells combined with dilated tubules and multiple calcium oxalate deposits are typical and completely in agreement with experimental studies reported by Byun and Kim (1998) in 10 dogs with ethylene glycol intoxication.

In conclusion, the timely detoxifying or antidote therapy with ethanol or 4-MP would prevent the renotoxicity syndrome, which is leading for this type of poisoning. We deem the detection of CRP in urine following ethylene glycol intoxication is an interesting and uncommon finding that confirms damaging of nephrons at glomerular level by the noxious substance as well. Using of CRP as a glomerular marker for early detection would enrich the diagnostic approach of that particular poisoning.

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