



ETHYLENE GLYCOL INTOXICATION IN A PREGNANT CAT AND A TOMCAT. CASE REPORT

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Summary

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Clinical cases of two cats, poisoned with ethylene glycol: one tomcat and a pregnant female in the last quarter of gestation, are presented. Cats were reared outdoor. The history included a sudden weakness, inappetence, lethargy and repeated vomiting in both animals. Physical examination showed reduced skin elasticity, hypothermia (37.3 C° and 37.8 C°), hyporeflexia, pale mucous coats. Blood biochemical changes comprised hyperglycaemia (7.74 and 10.1 mmol/L), hyperphosphataemia (6.3 and 5.67 mmol/L), increased urea (66.6 and 68.2 mmol/L) and creatinine concentrations (1408 and 918 µmol/L). Ultrasound examination showed severely increased corticomedullary echogenicity of kidneys, including foetal kidneys. Blood sample obtained *post mortem* from foetuses was characterised with dramatically increased phosphate (11.3 mmol/L), urea (66.2 mmol/L) and creatinine concentrations (642 µmol/L). Foetal urine had abundant calcium oxalate monohydrate crystals. Such crystals were present also in histological preparations from kidneys of both adult cats and foetuses.

Key words: cat, ethylene glycol, poisoning, pregnancy

Ethylene glycol is a dihydroxy alcohol (HO–CH₂–CH₂–OH), with broad household and industrial applications. It is the main component of antifreeze (67%), used in automotive, transport and aviation industries. It is also included in the composition of home cleaning products, varnishes and cosmetics. Pure ethylene glycol is a colourless, odourless liquid with sweetish taste (Leth & Gregersen, 2005; Traykova *et al.*, 2009). Due to its sweet

taste and being easily available, ethylene glycol poisoning in dogs and cats is among most commonly encountered intoxications during the last years (Schweighauser & Francey, 2016). Poisoning occurs most frequently after oral ingestion of ethylene glycol (antifreeze). In rare cases, it could occur after inhalational or percutaneous penetration (Upadhyay *et al.*, 2008). The substance is rapidly absorbed in the body, with peak levels 1 to 4 h after

ingestion, and almost half of ingested amount is eliminated unchanged via the kidneys. Under the action of alcohol dehydrogenase, ethylene glycol is converted to four highly toxic compounds: glycolaldehyde, glycolic acid, glyoxylic acid and oxalic acid (Leth & Gregersen, 2005). These compounds are cellular toxins which inhibit metabolism, cause central nervous system depression, metabolic acidosis, and substantial damage to the heart, gastrointestinal tract and the liver. The effects on renal parenchyma are the most fatal, with development of acute renal failure (Rusenov *et al.*, 2014.). The lethal dose for cats is 1.5 mL/kg, and for dogs: 4.4–6.6 mL/kg (Muresan *et al.*, 2008; Rusenov *et al.*, 2014). Death rates are exceptionally high: from 70–88% in dogs to 96–100% in cats (Hristov *et al.*, 2005; Popa *et al.*, 2018). Ethylene glycol intoxications are more commonly encountered in dogs than in cats, however, percutaneous absorption during grooming manipulations are more frequently reported in cats (Popa *et al.*, 2018). Accidents are more frequent during the autumn, winter and spring (Schweighauser & Francey, 2016).

Case description

Disease history: Two mixed-breed cats, male and female, one year of age and weighing about 3 kg, were referred to the Small Animal Clinic of the Faculty of Veterinary Medicine, Trakia University –

Stara Zagora in April 2017. Animals belonged to a private owner living in a village, and had free outdoor access. About 24 hours before the visit to the clinic, both cats suddenly stopped eating, became lethargic, apathetic and vomited several times.

Clinical data: Physical examination of both patients (day 0) showed average body build and good body condition. Cats were apathetic, weak, with decreased skin elasticity, pale mucous coats, weakened and slow reflexes. The main vital parameters of the tomcat were body temperature (BTT) 38.3 °C, heart rate – 140 min⁻¹ and respiratory rate 30 min⁻¹. BTT of female cat was 37.8 °C, heart and respiratory rates: 132 and 30 min⁻¹ respectively. Lung and heart auscultation of both cats showed no abnormal noises. Abdomen of both cats was flat, firm and painful at palpation. Frequent vomiting attempts were noticed. The female cat was in advanced pregnancy, about 50th–60th gestational day.

Diagnostics: Red and white blood pictures in the two cats showed no considerable deviations from reference ranges (Table 1).

Blood biochemical parameters were assayed twice and showed severe alterations (Table 2). Total protein and albumin remained within the reference ranges, blood glucose was slightly increased, serum calcium – slightly reduced with tendency to normalisation during the second blood analysis. Among liver enzymes,

Table 1. Red and white blood picture

	Haemoglobin, g/L	Red blood cells, T/L	Haematocrit, %	White blood cells, G/L	Platelets, G/L
Male cat	142	8.20	34.0	8.5	399
Female cat	102	6.88	28.6	12.8	634
Reference*	98–154	5.0–10.0	30–45	5.5–19.5	300–800

* Fielder (2015a).

Table 2. Blood biochemical profile

	Male cat		Female cat		Reference*
	day 0	day 1	day 0	day 1	
Glucose, mmol/L	7.74	–	10.1	–	3.3–6.7
Urea, mmol/L	66.6	62.9	68.2	65.3	6.8–12.1
Creatinine, μ mol/L	1408	1791	918	1162	80–194
Total protein, g/L	74.8	–	–	–	60–79
Albumin, g/L	31.2	–	34.5	–	28–39
ASAT, mmol/L	54	–	27	10	7–38
ALAT, mmol/L	132	493	37	800	25–97
ALP, mmol/L	60	142	31	130	0–45
Calcium, mmol/L	1.95	3.03	1.84	2.17	2.2–2.9
Phosphorus, mmol/L	6.3	8.55	5.67	9.02	1–2.0
Chlorides, mmol/L	93	69	101	71	115–130

* Fielder (2015b).

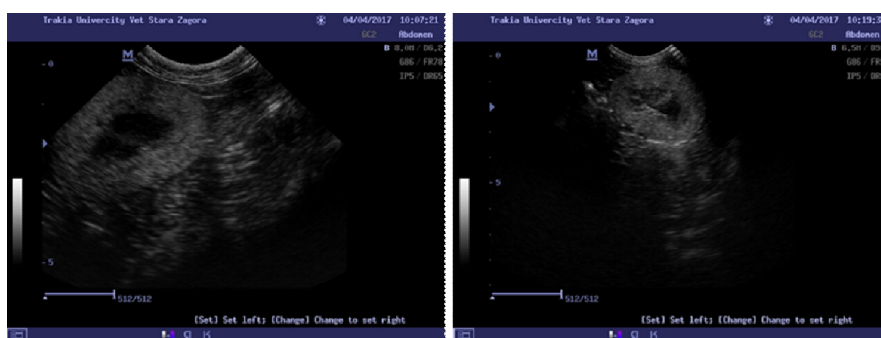


Fig. 1. Ultrasonograms of kidneys – adult cats.

ASAT was within the physiological range, yet ALAT and alkaline phosphatase activities during the second analysis were highly elevated. Most dramatic changes were observed in blood urea, creatinine and phosphorus, which were multifold higher. Four of assayed blood indices (creatinine, phosphorus, ALAT and chlorides) showed a clear trend to progressive increase (reduction for chlorides) between both samplings.

Echography revealed slightly enlarged kidneys in both cats with dramatically increased cortical and medullary echogenicity (Fig. 1).

Similarly, foetal kidneys (Fig. 2) de-

monstrated increased echogenicity of the renal cortex and renal pelvis.

Urinalysis findings consisted of high-grade proteinuria (+++), haematuria (++) , pyuria (+), density 1.038 and acid urine pH (5.2). The sediment contained kidney epithelial cells, erythrocytes, leukocytes, and multiple calcium oxalate mono- and dihydrate crystals (Fig. 3).

The analysis of data from all haematological, blood biochemical and ultrasound parameters were suggestive and largely supportive for the renal metabolic stage of ethylene glycol intoxication. Therapy with furosemide, Ringer solution, sodium bicarbonate 8.4% solution, calcium gluconi-

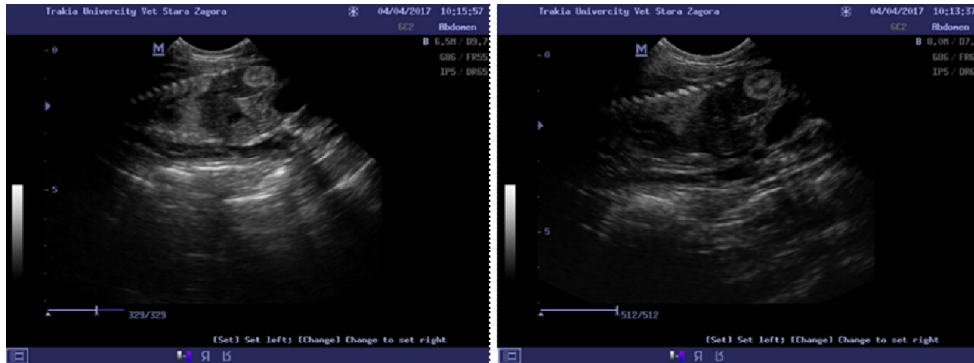


Fig. 2. Ultrasonograms of foetal kidneys.

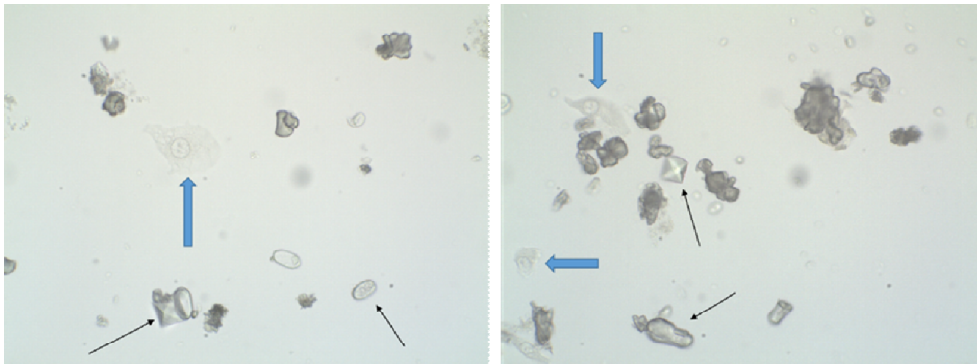


Fig. 3. Urinalysis findings. Calcium oxalate monohydrate and dihydrate crystals (thin arrows) and epithelial cells (thick arrows).

cum, metoclopramide, famotidine, vitamin B1 and enrofloxacin 5% (Baytril 5%) was prescribed.

On the next day (day 1) the clinical state of cats was progressively exacerbated, with more severe hypothermia (35.8 °C for the tomcat and 36.3 °C for the female cat), accelerated heart rate (162 min⁻¹ for the tomcat and 158 min⁻¹ for the female) and respiratory rate (46 and 44 min⁻¹ respectively). The animals were prostrated, with hypoesthesia and hyporeflexia. Blood biochemical profile parameters (Table 2) showed worsening of liver and renal functions as well as se-

vere electrolyte disturbance. The two cats died during the therapy, three hours apart.

During the necropsy, samples were collected from kidneys of adult cats and foetuses, amniotic fluid, urine and bulked blood sample from foetal heart ventricles for histopathological examination. Specimens were fixed in 10% neutral formalin and processed routinely (Dzhurov *et al.*, 1989). Cross sections of 4 µm thickness were stained with haematoxylin/eosin (H/E).

Macroscopically, changes in adult cats were similar: paler enlarged heart with dilated left atrium. The spleen was slightly

enlarged. Lungs were mildly hyperaemic. Small haemorrhages were observed on gastric mucosa, along with haemorrhagic inflammation of the duodenum. Kidneys were hyperaemic (Fig. 4).

Histopathologically, numerous transparent-yellowish crystals were present in renal tubules. In some areas, they were single, in others had irregular rhombus shape, and in third – were arranged in rosette-like structures compressing renal tubular epithelial cells (Fig. 5).

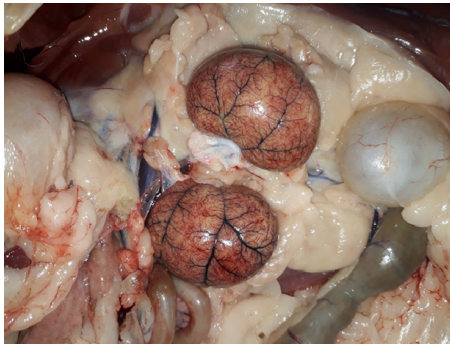


Fig. 4. Pathoanatomical finding. Hyperaemia of renal blood vessels.

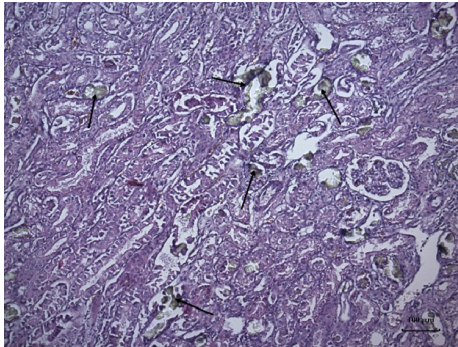


Fig. 5. Transparent-yellowish crystals in renal tubules (arrows). Haematoxylin/eosin, bar = 100 μ m.

Kidneys of adult cats and foetuses revealed severe degenerative changes (gra-

nular and fatty dystrophy) with hyaline casts and haemorrhages on occasional loci. The presence of calcium oxalate crystals was the cause for necrosis of some renal tubular epithelial cells. In some zones, mononuclear proliferations (lymphocytes and histiocytes), fibrous tissue (oxalate necrosis) and haemorrhages could be seen (Fig. 6).

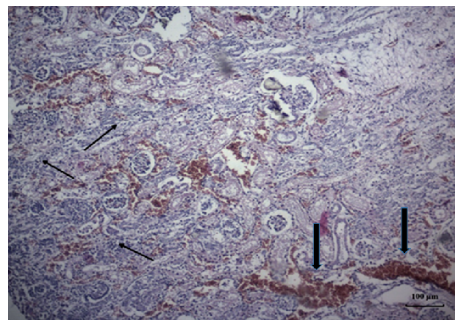


Fig. 6. Mononuclear proliferates (thin arrows) and haemorrhages (thick arrows). Haematoxylin/eosin, bar = 100 μ m.

The results from urinalysis of foetal samples demonstrated haematuria (++) , proteinuria (+), glucosuria (6 mmol/L), density 1.025 and acidic pH (5.5). Microscopic examination of the sediment showed numerous calcium oxalate monohydrate crystals and a plenty of epithelial cells from urinary ducts and renal parenchyma (Fig. 7).

The analysis of bulked foetal blood sample showed severe hyperphosphataemia (11.3 mmol/L), high urea (66.2 mmol/L) and creatinine (642 μ mol/L).

Once it entered the body, ethylene glycol is rapidly absorbed to attain peak blood plasma concentration within 1–4 hours. It does not bind to serum proteins and is converted mainly in the liver (80%) (Traykova *et al.*, 2009). After absorption, ethylene glycol is oxidised by nicotinamide adenine dinucleotide (NAD)-depen-

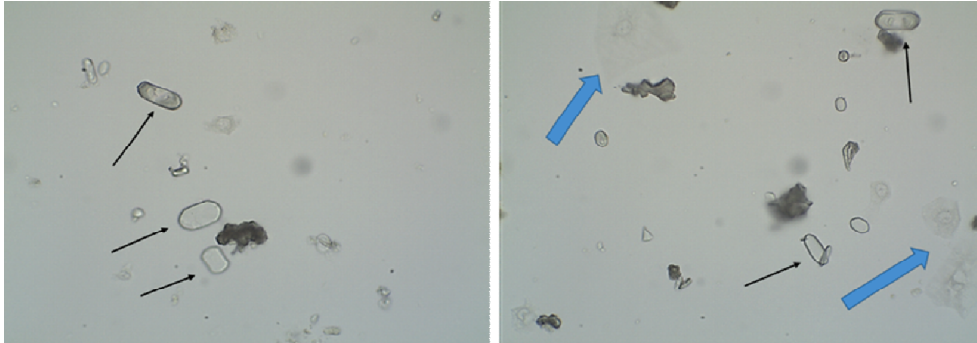


Fig. 7. Foetal urine sediment: calcium oxalate monohydrate crystals (thin arrows) and epithelial cells (thick arrows).

dent alcohol dehydrogenase in the liver and kidneys. Produced glycolaldehyde is additionally oxidised by mitochondrial aldehyde dehydrogenase and cytosol aldehyde oxidase to glycolic acid. The latter is further oxidised to glyoxylic acid, converted by oxidase to oxalic, formic and hippuric acid (Wu *et al.*, 2017) The limiting stage of ethylene glycol metabolic rate is the conversion of glycolic acid into glyoxylic acid. This results in accumulation of glycolic acid in blood with development of severe metabolic acidosis, and oxalate is precipitated in renal tubules as calcium oxalate (Sheta *et al.*, 2018). The acute intoxication occurs in three clinical stages: the first stage – general toxicity (30 min to 12 h after ingestion) is characterised with neurological (depression or euphoria, ataxia, hyporeflexia, convulsions) and gastrointestinal (nausea, vomiting, inappetence polydipsia) signs provoked by CNS intoxicating alcoholic effect of ethylene glycol and direct impact on gastrointestinal mucosa. The second stage (12-24 h after intake) is determined by occurring metabolic acidosis and cardiopulmonary signs. The third stage (24-72 h) is associated with deposition of calcium oxalate crystals in kidneys and de-

velopment of acute renal failure and severe azotaemia (Popa *et al.*, 2018). the appearance of oxalates in urine could occur within 4 to 8 hours after ingestion of ethylene glycol, but this is largely dependent on intoxication course and applied treatment (Wollersen *et al.*, 2009).

The presented clinical case describes the renal stage of ethylene glycol intoxication. Signs of progressing acute renal and liver failure and electrolyte disbalance result from the influence of toxic metabolites of ethylene glycol (Rusenov *et al.*, 2014; Song *et al.*, 2017). Observed gastrointestinal signs – vomiting, arexia and haemorrhages on gastric and duodenal mucosa are due both to the direct irritation of ingested ethylene glycol and uraemic toxins produced consequently to acute renal failure (Achappa *et al.*, 2019). The manifestations of lethargy, muscle weakness, tachycardia, tachypnea are associated with developing metabolic acidosis (Singh *et al.*, 2016). The deposition of calcium oxalate monohydrate crystals within renal tubules causes acute tubular necrosis and onset of acute renal failure with dramatic increase in blood urea, creatinine and inorganic phosphate concentrations (Takahashi *et al.*, 2008). Bind-

ing of oxalic acid to serum calcium during the third stage of the intoxication presumes the development of hypocalcaemia. The studies of Hodgman *et al.* (2017) refuted this statement and confirmed that hypocalcaemia in ethylene glycol poisoning is a rare sign, even in patients with metabolic acidosis. Their thesis is fully supported by the present case report, where hypocalcaemia was low-grade and fast transient. The presence of specific calcium oxalate monohydrate crystals in urine confirmed data from the clinical exam and blood analysis in ethylene glycol intoxications (Sheta *et al.*, 2018; Salem *et al.*, 2017). The occurring specific echographic changes with kidney hyperechogenicity are also a direct effect from the precipitation of crystals in renal tubules and oxalate crystalluria (Rusenov *et al.*, 2014). The documented histopathological alterations (degeneration, haemorrhages, necrosis of kidneys and deposition of oxalates in them) are closely related to toxic effects of ethylene glycol metabolites.

The information about the course of ethylene glycol poisoning in pregnant females is exceptionally scarce. There are no data about the toxicokinetics and effects of ethylene glycol and its metabolites on foetuses. The fact that foetuses exhibited the same haematological, urological, ultrasonographic and histopathological changes observed in adult cats (hyperphosphataemia, uraemia, oxalate crystalluria, renal hyperechogenicity) confirmed the ability of ethylene glycol to pass the placental barrier leading inevitably to fatal outcome. In our belief, the described changes in blood parameters, urine, kidney echogenicity and histopathological findings in feline foetuses throw light on toxicokinetics, spread of toxins in the body and their effects in pregnant animals.

The reported changes add to the clinical experience related to ethylene glycol intoxication in dogs and cats.

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