Pebble’s Poison

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The following details the typical clinical presentation and management of canine patients with ethylene glycol (antifreeze) induced toxicity and follows a case of Ethylene Glycol toxicity. Ethylene glycol is the primary ingredient in many automobile anti-freeze products, but is also found in color film processing fluids, industrial solvents, and some rust removers[9]. It is reported to be sweet to the taste and is odorless, which may encourage consumption by domestic animals[8]. Ethylene glycol is not toxic on its own, but produces marked metabolic acidosis and renal injury after being metabolized in the liver[1]. In the US alone the estimated average of ethylene glycol toxicity in dogs ranges from 10,000 to 45,000 cases per year[9].

Presentation

Ethylene glycol toxicity can happen at any time of the year, but is most commonly seen in late fall and early spring[5]. During this time many drivers are handling, and possibly poorly disposing of, antifreeze for their vehicles. In fortunate cases, the owner notices their dog drinking the anti-freeze and takes them to a veterinarian. In less fortunate cases the owner may simply notice clinical signs and become concerned.

In this case, Pebbles, a 3 year old female spayed German Shepherd dog; presented to the emergency service for ataxia and vomiting. Pebbles is an indoor-outdoor dog who had been in the yard most of the day. Early in the day Pebble's owners noticed their other dog vomiting up what appeared to be chicken bones. After walking the perimeter of the backyard, a bag containing partially eaten chicken was found. The chicken was disposed of and the other dog showed no further clinical signs. Later that day, when both dogs were called in for their evening meal, Pebbles was acting agitated and displaying ataxia (which the owner's described as appearing drunk). She then vomited and fell down the stairs, at which time she was brought in

for treatment. The owner's stated that they believed a neighbor may have poisoned the chicken previously found in the yard.

The typical clinical signs of patients suffering ethylene glycol toxicity are dependent on stage at which the animal is presented. Peracute signs of toxicity (within the first 12 hours) can include vomiting, ataxia (often described as drunk by owners), polydipsia, polyuria, agitation, CNS depression, and seizures[5]. As the liver metabolizes the ethylene glycol, these signs will resolve and signs of acute renal injury will predominate, including: polyuria and polydipsia progressing to oliguria, dehydration, and hypovolemia[8]. Uremia may also lead to bloody vomiting and diarrhea[5]. Cardiovascular signs include tachypnea and tachycardia[7].

Clinical lab findings associated with ethylene glycol toxicity include metabolic acidosis, azotemia (pre-renal or renal, depending on stage of toxicity), hyposthenuria, and presence of calcium oxalate monohydrate crystals in the urine. If the patient presents in acute renal failure, lab findings may also include hypocalcemia, hyperphosphatemia, and hyperkalemia[6].

On presentation Pebbles was anxious, alert, and responsive. Her pulse was elevated at 156 beats per minute and her temperature was mildly elevated at 102.5. She was panting heavily and hypersalivating. The remainder of her physical exam was within normal limits. A neurological exam found no proprioceptive deficits, ataxia, or weakness.

Pathophysiology

The pre-metabolized ethylene glycol exerts effects on the body very similar to ethanol, causing CNS depression and ataxia. Additionally, ethylene glycol is believed to inhibit anti-diuretic hormone in a similar fashion to ethanol, leading to polyuria, polydipsia, and hypovolemia. When it has reached the liver, Ethylene glycol is metabolized by alcohol

dehydrogenase to the intermediates glycolic acid, glyoxylic acid, and finally oxalic acid[9]. Accumulation of these acids in the blood stream causes a metabolic acidosis, which drives the oxalic acid to chelate circulating calcium and form calcium oxalate monohydrate crystals.

Calcium oxalate monohydrate crystals then pass freely through the glomerulus of the kidney to the proximal tubules, where they lodge and damage proximal tubular cells directly. Several mechanisms of damage to the proximal tubules have been proposed: attachment to plasma membrane leading to damage, activation of damaging enzymes, and oxidation of lipid membrane, but none have been confirmed[3]. Additionally, crystals can accumulate in the tubules to such an extent as to completely block flow of urine. Crystals may also be found in the meningeal vessels, but do not appear to damage the meninges[5]. As the calcium oxalate monohydrate crystals accumulate in the proximal tubules, the damaged cells become unable to concentrate appropriately, leading to acute renal injury and possible failure.

Differentials:

Alternative differentials for the clinical signs of peracute ethylene glycol toxicity should include trauma, ethanol consumption, hepatic encephalopathy, heat stroke, and intracranial neoplasia[10]. Differentials for acute renal failure include: nephrotoxic medications (chemotherapeutics, immunosuppressants, antimicrobials, and NSAIDs), toxins (cholecalciferol, raisins/grapes, heavy metals, amanita mushroom), infectious diseases (leptospirosis, lyme), thromboembolic diseases, urinary obstruction, and heat stroke[9].

Differentials for Pebbles at the time of presentation included those listed for peracute signs, as well as differentials for vomiting such as a foreign body, dietary indiscretion, gastric

ulcers, pancreatitis, gastritis, and many others. Following initial diagnostics (detailed under diagnostic section), differentials were amended to include those listed for acute renal injury.

Diagnostic Approach

In cases where ethylene glycol toxicity is suspected, definitive diagnosis can be obtained with serum ethylene glycol levels. The lethal serum concentration for dogs is 50 mg/dl and levels as low as 20 mg/dl can be detected with commercially available serum tests[7]. These tests may not be available to every practitioner or may be a send out test, which makes them more useful as confirmatory tests than point of care diagnostics. Therapy should be initiated immediately and aggressively while waiting for test results. Calcium oxalate monohydrate crystals can be found in the urine as early as 2 hours post ingestion. Some anti-freeze products contain fluorescein stain, which is excreted in the urine and will fluoresce under a wood's lamp, however this is not a reliable test 6 hours past ingestion and some medications can also cause urine to fluoresce[7].

Ultrasound of the kidneys may reveal a hyperechogenic cortex (nephrocalcinosis), which in conjunction with the previously mentioned clinical signs should increase suspicion of ethylene glycol, but is not definitive. Gross post-mortem evaluation typically reveals pulmonary edema, petechiae, stomach contents that resemble coffee grounds, pale and soft myocardium, enlarged spleen, and pale wrinkled kidneys[5]. Microscopically, calcium oxalate crystals can be found in the tubules along with tubular epithelial necrosis[5].

Pebbles blood was drawn for a complete blood count, chemistry panel, coagulation profile, and blood gas analysis; urine was collected for a urinalysis. CBC was unremarkable. Chemistry panel revealed mild hypernatremia, mild hyperchloremia, moderately low CO2, mildly elevated creatinine, and mild hyperphosphatemia. Coagulation panel was within normal

limits. Blood gas analysis found a metabolic acidosis with respiratory compensation. A urinalysis found no protein or glucose, but a moderate amount of calcium oxalate-monohydrate crystals, solidifying a diagnosis of Ethylene Glycol toxicosis.

Pebbles was hospitalized for fluid diuresis and given supportive care (pantoprazole, activated charcoal administration, and gabapentin).

Abdominal radiographs were taken and found bony fragments in the stomach and small intestine. Follow up with abdominal ultrasound revealed a mildly enlarged spleen, hyperechoic renal cortices, and soft tissue opaque material in the stomach causing distension. Endoscopy was performed to remove the foreign material seen on radiographs and prevent possible obstruction. Pebble's stomach contained ingesta and pieces of plastic, which were removed and sent for ethylene glycol testing at owner request.

Treatment

Vomiting can be induced in acute toxicities where consumption of ethylene glycol was witnessed or is highly suspected[6]. Vomiting may not prove an efficacious therapy if ingestion occurred more than a few hours prior to presentation. Vomiting was not induced in Pebble's case as she had already vomited at home and it had now been several hours since suspected toxin exposure.

The treatment of choice for ethylene glycol toxicosis is 4 methylpyrazole in addition to aggressive fluid therapy. 4 methylpyrazole (4-MP) inhibits the activity of alcohol dehydrogenase in the liver, preventing conversion of ethylene glycol to oxalic acid[4]. Un-metabolized ethylene glycol can be safely excreted by the kidneys without causing tubular damage. 4-MP can be

expensive and is cost prohibitive for many owners. In the case where 4-MP is unavailable or unaffordable, IV ethanol is an acceptable alternative. Ethanol competes with ethylene glycol for, and has a higher affinity to, alcohol dehydrogenase. While ethanol occupies the alcohol dehydrogenase, the kidneys may safely excrete the ethylene glycol as with 4-MP. Caution should be taken when using ethanol since it causes CNS depression, polyuria, polydipsia, and hypovolemia[4]. 4-MP or ethanol treatment was not initiated for Pebble's as her peracute clinical signs had already resolved at presentation and ethylene glycol was not confirmed until urinalysis results came back. At this time the toxin was likely already metabolized and causing damage; supportive care and fluid diuresis were indicated.

Hemodialysis can remove urea, ethylene glycol, and ethylene glycol metabolites directly and is very effective if initiated within 8 hours of toxin consumption[8]. This treatment is typically accompanied by administration of 4-MP or ethanol. Hemodialysis was not available in Pebble's case without referral, which the owner declined.

Fluid diuresis is a mainstay of treatment for any acute kidney injury. It is critical to maintain blood volume and renal perfusion, as well as aid in correction of the metabolic acidosis caused by the metabolites of ethylene glycol[6]. LRS and Plasma-Lyte are both appropriate choices[6]. High administration rates are often necessary to maintain glomerular filtration rate, thus all patients should be monitored for signs of fluid overload and rates may need to be decreased for oliguric dogs. To assess for urine output, an indwelling urinary catheter should be placed for measuring of ins and outs. Alternatively, patients may be weighed regularly to assess for fluid overload. Fluid diuresis should be continued until azotemia resolves.

Pebbles remained hospitalized receiving IV LRS and supportive care. Serial renal panels were run daily and fluids adjusted appropriately. She was slowly weaned off of fluids when her

creatinine remained normal. Her renal values remained normal after discontinuing fluids and she was discharged on day five of hospitalization.

Prognosis

The prognosis for untreated ethylene glycol toxicity is poor to grave[6]. Prognosis for animals who receive appropriate treatment is variable and dependent on the animal's condition at presentation as well as how much time has elapsed since ingestion. Negative prognostic indicators include: oliguria, hypocalcemia, hyperphosphatemia, and severe azotemia[6].

Pebbles prognosis was greatly improved due to prompt action by the owner and early fluid diuresis maintaining renal perfusion. Additionally, it was suspected that she received a relatively low dose of toxin, although her blood levels were never measured. The results of the ethylene glycol test from the ingesta returned as positive for exposure two days after her discharge.

Pertinent information

Anti-freeze products labeled as non-toxic are available for purchase. These products contain propylene glycol instead of ethylene glycol and do not result in formation of oxalic acid or calcium oxalate monohydrate crystals. However, dogs who consume sufficient amounts may show similar signs to the acute phase of ethylene glycol toxicity[2]. Supportive care is sufficient treatment for dogs with propylene glycol toxicity.

Citations

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