Nephrotoxic Metals and Inorganics  (9-Aug-1999)

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Chapter Sections
Cadmium
Zinc
Boric Acid and Borate
Other Nephrotoxic Metals

Cadmium

Sources

- Artists' paints.
- Cadmium is a metal which has become an environmental contaminant as a result of effluents from plants smelting zinc, copper and lead, as well as from industries using cadmium in batteries, alloys and paints. Environmental contamination is very important since cadmium is one of the most biocumulative metals.
- Cadmium (and lead) are often components of municipal sewage sludge in many communities in which the appropriate industries are located. This sewage sludge has, at times, been sold or given away as a soil amendment for agricultural or home gardening applications. Commercial sludge may contain up to 1500 mg of cadmium per kg dry material.
- Cadmium added to soil tends to be taken up into the leafy portions of plants, but may sometimes reach toxic concentrations in grains as well.
- Cadmium-containing fungicides were once used on turf grass. Cadmium chloride was sometimes used for this purpose, a concentrated form of which contained 12.5\% elemental cadmium. Trade names included Caddy® and Vi-Cad®.
- Cadmium succinate was also used on turf grass as a fungicide and the concentrate contained 29\% elemental cadmium. The trade name was Cadminate.
- Other turf grass fungicides contained mixtures of cadmium, calcium, copper, zinc and chromates. Trade names included Miller 531®, and Crag Turf Fungicide 531®.

Toxicity

- A rat oral LD50 of cadmium chloride was 88 mg/kg.
- A rat oral LD50 of cadmium succinate was 660 mg/kg.
- Long-term effects of low-level exposure to cadmium include renal tubular disease, chronic obstructive pulmonary disease, and emphysema. Respiratory effects have been noted following inhalatory exposure.

Mechanisms of Action

- Cadmium inhibits enzymes associated with zinc and displaces it from metalloenzymes. Cadmium also inhibits zinc uptake by the male reproductive tract.
- Chronic cadmium toxicosis causes increased likelihood of copper and iron deficiencies, blocks renal synthesis of the active form of vitamin D, and results in anemia, growth inhibition and poor bone mineralization.
Low levels of dietary protein, calcium, iron, or zinc cause increased cadmium absorption. Young absorb more than adults.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Two to 8% of ingested cadmium is absorbed on a chronic exposure basis, and a fraction of the absorbed cadmium is initially retained in the liver and then redistributed, especially to the kidneys.
- The absorbed cadmium is eliminated in the feces via the glands of the stomach, intestine and pancreas.
- Cadmium induces metallothionein, a metal binding protein. Metallothionein also binds zinc, copper, and iron. Metallothionein binds cadmium to protect organs from exposure to the metal, but the Cd-metallothionein complex is taken up by the kidney, and this enhances nephrotoxicity.
- After large amounts accumulate in the kidneys, renal damage occurs and only then does urinary excretion result and the renal concentration falls.

Clinical Signs

- In chronic exposure in man, renal damage, bone deformities, osteoporosis, spontaneous fractures and anemia occur.
- Cause of itai itai (translation, ouch, ouch) disease in Japan. This disease was associated with the ingestion of cadmium-contaminated rice and is characterized by acute pain and deformity from spontaneous fractures. Women (especially those which had several children) were more susceptible.
- Acute oral exposure to high concentrations may cause excessive salivation, persistent vomiting, diarrhea, abdominal pain, ataxia, loss of consciousness, severe gastroenteritis, subdural hemorrhage and testicular necrosis.
- Inhalation of cadmium is generally characterized by dyspnea, cough, fever, and pulmonary edema.

Diagnosis

- Liver, kidney, and/or blood calcium.
- Horses tend to have much higher cadmium (in normal animals) than with other domestic species.
- Appropriate history, clinical signs, histologic changes in the kidneys, bone, gut, etc.

Treatment

- For acute toxicoses, BAL and calcium EDTA decrease mortality, but for chronic toxicoses are generally ineffective and may increase cadmium concentrations in the kidney, BAL is considered contraindicated after chronic exposure due to increased risk of nephrotoxicity.
- Efforts to remove cadmium from the digestive tract should be employed in recent exposures.
- In cases of chronic exposure, supplementation with zinc, copper and iron in more than normally adequate amounts are significantly protective. Vitamins C and D, cysteine and selenium also aid in protection. Naturally, steps to terminate exposure should be instituted.

Comment

Cadmium is rarely recognized as a toxicant in veterinary practice.

Zinc

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, seals, caged birds, ostriches</td>
<td>Days</td>
<td>Days to permanent damage; often lethal</td>
</tr>
</tbody>
</table>

Sources

- Zinc toxicoses have recently been reported in dogs as a result of ingestion of zinc nuts from hardware used on transport cages or those in veterinary facilities or from repeatedly licking off zinc oxide ointment (often Desitin) used to treat skin lesions.
- Ingestion of pennies.
  - **Note** - Pennies minted beginning in 1983 (and some from 1982) contain 99.2% zinc and 0.8% copper by weight (pennies weigh 2.5 grams each).
Poisoning reported in human beings and animals from drinking water (especially when it's acidic) from galvanized tanks. Poisonings have been reported as a result of ingestion of acidic food or beverages from galvanized containers. Birds may ingest zinc from "welded wire" fencing. "Metal fume fever" reported to occur in industrial workers exposed to zinc vapors. This syndrome is characterized by pulmonary manifestations, fever, and gastroenteritis.

Susceptible Species

Poisonings described in dogs, cats, ferrets, mink, sheep, horses, cattle, caged birds, and ratites.

Toxicity

- Zinc at 500 - 1,500 ppm in diets fed to ferrets resulted in diffuse nephrosis; and 3,000 ppm dietary zinc was lethal.
- An acute oral LD50 for zinc chloride was 96 mg/kg in the guinea pig.
- Rats, pigs, and poultry tolerate dietary levels of 1,000 to 2,000 ppm without adverse effects.
- Cattle and sheep have decreased feed consumption when the diet exceeds 1,000 ppm zinc.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

- Zinc is excreted primarily via the bile and pancreas.
- Chronic zinc toxicosis interferes with absorption and utilization of iron and copper.
- Mucosal irritation can result from ingestion of certain zinc salts (e.g., zinc oxide).
- Approximately 2/3 of the zinc in serum or plasma is loosely bound to protein and the remainder is tightly bound.

Clinical Signs

- Single ingestions of zinc oxide ointment are characterized mainly by vomiting.
- Subacute or chronic zinc toxicosis primarily affects the renal, hepatic, and hematopoietic tissues.
- The most common clinical signs in small animals include: vomiting, anorexia, hemoglobinuria, diarrhea, weakness, icterus. Can also see clinical signs (e.g., oral ulcers) associated with acute renal failure.
- Cattle may present with anorexia, depression, polydipsia, polyphagia, decreased milk yield, chemosis, exophthalmia, convulsions, and death.

Clinical Pathology

- Regenerative anemia; hemolytic anemia with hemoglobinemia and hemoglobinuria possible.
- Increased serum alkaline phosphatase, bilirubinemia.
- Hypophosphatemia, isothenuria or hypothenuria, proteinuria, hematuria, azotemia, and renal casts all consistent with acute renal failure.
- Lesions.
  - Hemorrhagic gastritis.
  - Proximal renal tubular epithelial necrosis.
  - Centrilobular hepatocyte vacuolization, necrosis of individual cells occurs. Bile casts in bile canaliculi.

Diagnosis

- Elevated serum, tissue (kidney, liver), and urine zinc concentration. Note: Special tubes for elemental analysis (Royal blue top) are recommended. In addition, syringes used in collecting blood should contain no rubber gromets (i.e., all glass or all plastic). This is necessary because certain blood tubes and syringes have zinc stearate present in the lubricant which can contribute up to 5 - 6 ppm extraneous zinc.
- Radiograph abdomen for presence of zinc hardware.
- Differential diagnosis-acute autoimmune hemolytic anemia.

Treatment

- Symptomatic and supportive therapy.
- Fluid for acute renal failure.
- Emetic if no contraindications exist.
• Gastrostomy or enterotomy may be required to remove zinc foreign bodies.
• Chelation therapy (CaEDTA or penicillamine) may be required.
• Give fluids and bicarbonate (slow IV) to help prevent renal failure if hemolysis is a problem. Blood transfusions may be indicated.

Boric Acid and Borate

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Nephrotoxic Metals and Inorganics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly pets</td>
<td>Hours to days</td>
<td>Days to weeks; toxicosis rare</td>
<td>deaths very rare</td>
</tr>
</tbody>
</table>

Sources

• Roach and ant poisons, which are often > 95% boric acid (often called ortho-boric acid), comprise the most common source causing toxicosis in small animals.
• The decahydrate of sodium borate (borax) is used in cleaning clothing in washing machines.
• Sodium perborate, which decomposes to form hydrogen peroxide and sodium borate, is found in denture cleansers.
• Whether sodium borate breaks down to boric acid is unknown.

\[
\text{OH} \rightarrow \text{B} \rightarrow \text{OH} \\
\text{OH} \quad \text{B}_4\text{Na}_2\text{O}_7 \\
\text{Boric Acid} \quad \text{Sodium Borate} = \text{Sodium Tetraborate}
\]

Toxicity

• Boric acid-oral LD₅₀ in the rat is 2.68 g/kg to 4.08 g/kg.
• Borate-oral LD₅₀ in the rat ranges from 4.5 - 4.98 g/kg.
• One gram of boric acid is roughly equivalent to 1.55 g borax.
• Sodium borate contains 21.50% boron.

Absorption, Distribution, Metabolism and Excretion (ADME) and Mechanism of Action

• Exact mechanism is unknown; generally cytotoxic to all cells.
• Soluble borates are absorbed from the gastrointestinal tract.
• Concentrated in the kidney before excretion; probably related to the fact that the kidney is the organ that is most damaged. Renal excretion is comparatively slow.

Signs

• Vomiting, diarrhea, anorexia.
• Muscle weakness and ataxia, possible hyperpyrexia.
• Seizures possible, tremors may be seen prior to seizures if they occur.
• Depression and lethargy.
• Oliguria or anuria, possibly hematuria, and albuminuria.
• Erythematous skin eruptions develop in humans (and pet monkeys) which may become generalized; may have a "boiled lobster" appearance.
• Metabolic acidosis may occur.

Lesions

Gastroenteritis, nephrosis, fatty degeneration of kidneys, hepatic damage, fatty degeneration of liver, possible cerebral edema.
Diagnosis

- Appropriate clinical signs and/or lesions with a history of sufficient exposure.
- A bench chemistry test is available for detecting boric acid in urine.
- Oliguria, anuria, proteinuria, casts and red blood cells.
- Chronic poisoning can occur.

Treatment

- For recent exposure, an emetic has been recommended or, if contraindicated, gastric lavage is suggested, either approach is followed by activated charcoal administration.
- Fluid diuresis, peritoneal dialysis, and/or exchange transfusions.
- Peritoneal dialysis has been shown to be effective in reducing blood levels of boric acid in human poisoning.
- Symptomatic treatment as necessary.
- Should seizures occur in dogs, diazepam is recommended.

Other Nephrotoxic Metals

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Poultry (nonlayers)</td>
<td>Chronic</td>
<td>Chronic; often lethal</td>
</tr>
<tr>
<td>Mercury</td>
<td>(See Toxicants with Mixed Effects on the Nervous System)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>(See Toxicants that Cause Hemolysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>(See Toxicants that Affect the Liver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uranium</td>
<td>(Toxicosis is rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>(Toxicosis is rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>(Toxicosis is rare)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources

- Mercury: See section on Mercury under the heading Toxicants with Mixed Effects on the Nervous System.
- Copper: Will be discussed in the section on agents causing hemolysis. The renal effects of copper are mediated in significant measure as a result of the effects of hemoglobin on the renal tubules. In short copper builds up in the liver until a critical concentration exists, then, usually after some external stress, liver failure and loss of the copper stored in the liver result in massive release of copper into the blood. The resultant hemolysis causes hemoglobinemia, which produces a tubular nephrosis and gun-metal colored kidneys. Hemoglobinaemia occurs and death is very common. By far, sheep comprise the most commonly affected species. The veterinary diagnostician considering copper toxicosis must remember the hepatotoxic, hemolytic, and nephrotoxic effects of chronic copper toxicosis as well as the possibility of gastrointestinal damage from acute exposure.
- Uranium: Acute renal damage may result when soluble uranyl ions are absorbed after oral ingestion or when uranyl nitrate is absorbed through damaged skin.
- Chromium: Sources include corrosion inhibitors, paints, drilling muds used in oil well exploration, inks and wood preservatives. Ashes from some treated lumber products may also be a source, although the primary toxicant in such cases is usually arsenic. Acute toxicosis is characterized by gastrointestinal irritation with ulceration, shock, liver injury and renal damage with tubular necrosis and albuminuria. Toxicosis may result from accidental mixing of chromium containing materials into feeds.
- Bismuth: The toxicity of most bismuth containing compounds available to animals is low. With massive doses, bismuth causes effects much like some of those caused by mercury: gingivitis, dermatitis, and kidney damage. As in the case of mercury poisoning, toxicosis due to bismuth may be treated with the chelator BAL. Commonly encountered bismuth containing medications include Pepto-Bismol®, which contains bismuth subsalicylate, but the primary concern with this product is due to salicylate, not bismuth toxicosis (see Aspirin and Salicylate handout). Another form used medically is bismuth subnitrate; and with sufficient exposure the principle toxicologic concern is nitrate poisoning rather than bismuth overdose. Other trivalent, insoluble bismuth salts are also used orally for diarrhea and other gastrointestinal distress syndromes, and these rarely result in toxic consequences. The kidneys excrete bismuth and can concentrate it in the proximal tubules where it causes degeneration and necrosis. Inclusion bodies in the proximal tubules can be noted.
References

Zinc


Boric Acid and Borate


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