Vitamin K₃ (Menadione)

Sources

- Vitamin K₃ is synonymous with menadione N.F., Menaphthone®, Panosine®, and Synkay®. Vitamin K₃ dimethyl pyrimidinol bisulfite is a related compound which is also called Hetrazene®. Vitamine K₃ sodium bisulfite, also called menadione sodium bisulfite, Hykinone®, Klotogen®, Clotin®, and Vicasol® or just Vitamin K₃®, is the actual form implicated in causing renal failure in horses. Menadione sodium diphosphate, USP, sometimes called Synkayvite® is also available.
- Whether forms of Vitamin K₃ other than the sodium bisulfite salt are similarly toxic has not yet been determined and, for the present, they are all best avoided.
- Vitamin K₄, also called menadione acetate, acetomenaphthone, Prokayvit®, and Kappaxin®, and vitamin K₄ sodium diphosphate, also known as menadiol diphosphate tetrasodium salt or Synkayvit®, are also considered suspect because of their structural similarity to Vitamin K₃.
Toxicity

- Initial recognition of an apparent toxic effect of vitamin K3 in the horse came about as a result of its empiric use to treat exercise-induced pulmonary hemorrhage or epistaxis in racehorses.
- Toxicosis may occur at the lowest recommended dosage of 2.2 mg/kg BW.
- The range of recommended dosages is from 2.2 - 11 mg/kg BW for the implicated vitamin K3 products.
- Dosage is recommended for these particular products by the intravenous and intramuscular routes. The influence of route of administration is not known, but one case of lethal renal failure occurred in a horse which was given a 3.75 mg/kg dose by the intramuscular route.
- The recommended total dose for man is only 2 - 10 mg.

Mechanism of Action

- Menadione sodium bisulfite causes hepatic and renal disease in rats. To date, in horses no hepatic lesions or dysfunction has been documented.
- In the rats, however, anemia, hemoglobinuria and urobilinogenuria also occurred.
- Similarly hemolytic anemia and kernicterus (severe jaundice and brain damage) in premature human infants has been observed following injection of large doses of menadione.
- Vitamine E-deficiency has been suggested as possibly playing a role in vitamin K3 toxicosis. In vitamin E-deficient premature infants or animals, auto-oxidation of vitamin K analogues may occur. It is postulated that auto-oxidation may (despite normal glutathione concentrations) result in membrane instability in the red blood cell with hemolysis which may result in hemoglobin-induced nephrosis. This theory must be tested further before it can be accepted or rejected.
- Hemolytic anemia has not been observed in the equine patient although there is evidence of hemolysis and hemoglobinuria. At this time, it appears that hemolysis is not the primary nephrotoxic mechanism in equine nephropathy.
- The effect of vitamin K3 in the horse is rapid with experimental horses exhibiting evidence of renal colic and hematuria within 4 - 12 hours.

Signs and Clinical Findings

- Onset of signs occurred in experimentally and otherwise dosed horses within 5 - 48 hours of injection of vitamin K3 in most horses.
- Depression was the first clinical sign noted in closely observed horses.
- Signs of colic: slightly arched stance, rubbing of perineum and tail head on the stall, looking at the flanks, lying down and getting up, and stranguria were frequently observed.
- Some horses were mistakenly believed to be experiencing intestinal colic, however, clinical pathologic information allowed recognition of the renal component.
- Moderate to greatly enlarged kidneys on palpation.
- Frank hematuria in some horses. Microscopic evidence of hematuria in most cases.
- Anorexia.
- Fever in some affected horses.
- Occasionally noted clinical signs include: hemolysis, hemorrhage, disseminated intravascular coagulation, vasculitis, laminitis, and dependent edema.
- Death may occur within a few days, horses may recover after a clinical course of 5 - 7 days or they may experience chronic renal failure in some cases.

Clinical Pathology

- Proteinuria.
- Hematuria.
- Fixed specific gravity values (1.009 - 1.013).
- Elevated blood urea nitrogen and creatinine which correlate with the severity of the syndrome in individual animals.
- Serum electrolyte values were consistent with renal tubular disease in horses and included: hyponatremia, hypochloremia and hyperkalemia and less often hypercalcemia during the acute renal disease.

Lesions

- Gross enlargement and paleness of the kidney, which bulges from the cut surface.
- Histologically diffuse or multifocal tubular necrosis and dilation.
- Proteinaceous and cellular debris from red blood cells and neutrophils and casts were present in renal tubules.
- In surviving animals renal tubules still exhibiting degeneration, necrosis and dilation may be present in scattered areas of the kidney at
3 months after dosing. In chronic renal failure following vitamin K₃ administration, the kidneys may be greatly reduced in size, the capsule adherent, and pale streaks of connective tissue may be grossly apparent. On microscopic examination, the connective tissue appears massive, and the glomeruli hypercellular, and/or sclerotic. The tubules are dilated but the lining epithelium appear normal. Mineral, cellular, and proteinaceous casts may be seen in many tubules. Chronic mononuclear cell infiltrates are commonly observed.

**Treatment**

- No specific treatment has been investigated. It is most important to avoid using vitamin K₃ or vitamin K₄ in the horse in the first place.
- Fluids, bicarbonate (to reduce hemoglobin deposition in renal tubules) and good supportive care are indicated.

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**Blister Beetle - Cantharidin Toxicosis**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Nephrotoxic Organic Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses, cattle, sheep</td>
<td>Hours</td>
<td>Few days; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Images**

- Black Blister Beetle, Epicauta spp. - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- Striped Blister Beetle, Epicauta spp. - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

**Sources**

- Blister beetle = Epicauta spp. Includes "striped blister beetle", black blister beetle, others. Aid to identification is that the prothorax or "neck" is narrower than the head.
- Blister beetles, as adults, are usually leaf or flower feeders.
- Another blister beetle species, pyrota insulata has been found to cause cantharidin toxicosis when ingested by emu chicks in Texas.
- Toxicosis is due to ingestion of blister beetle itself.
- Problems occur primarily when beetles are present in alfalfa hay-southwestern U.S., plains states, occasionally in Illinois, Midwest, East.
- Increased incidence due to simultaneous cutting and crimping hay.
  - Separate cutting (traditional process) allows beetles to leave or settle out.
  - Found in alfalfa that is harvested at flowering.
- Over 100 beetles have been taken from 1 flake of hay.
- Spanish fly = cantharidins.

**Cantharidin**

**Toxicity**

- Cantharidin, bicyclic terpenoid, contained in the hemolymph, genitalia, and other tissues of beetle.
- Experimental feeding of crystalline cantharidin, at 489 - 720 µg/kg to horses, resulted in clinical signs of cantharidiasis and deaths.
- Toxicity of beetles varies, 4 - 6 grams air-dried ground beetles may be fatal.
- In some studies 30 beetles were lethal for a horse.
Mechanism of Action

- Unsure, strong mucosal irritant, causes hypocalcemia by an uncertain mechanism.
- Ingested cantharidin causes irritation of oral and GI mucosa leading to colic.

Susceptible Species

- Horses, cattle, rabbits, goats, and sheep reportedly poisoned by oral ingestion of beetles.
- Primarily horses, less often cattle.
- Morbidity ranges from sporadic to 100%.
- Other species including mice, rats, and dogs have been experimentally poisoned with ingestion of ground beetles or cantharadin.

Signs

- Variable, depends on dosage.
- Massive exposure can cause severe shock and death within hours-lethally affected animals die within 3 days.
- Mucous membrane irritant-severe oral, GI, and urinary tract inflammation and ulceration.
- Animals urinate frequently, rub perineum, exhibit prolonged episodes of repeated tenesmus.
- Colic, variable effects on intestinal motility.
- Hypocalcemia-synchronous diaphragmatic flutter = contraction of diaphragm with each heart beat (some persons may call this effect "thumps"). Hypocalcemia may be related to myocardial damage and/or shock.
- Listlessness.
- Rapid thready pulse (HR).
- Hemoconcentration with low urine specific gravity.
- Cyanosis, muddy mucous membranes.
- Rapid, shallow respiration, acidosis is not usually a feature.
- Shock and death.

Clinical Pathology

- Many observed changes in blood chemical parameters parallel those seen with colic, monensin toxicosis, and endotoxic shock.
- However, reduced total plasma calcium and magnesium concentrations in cantharidiasis help to differentiate this syndrome from other colic-like diseases and monensin toxicosis. Hypocalcemia and hypomagnesemia may last 1 - 2 days.
- Elevated BUN (variable).
- Leukocytosis.
- Hemoconcentration.
- Low urine specific gravity for the first day in spite of the hemoconcentration.

Lesions

- Confined to GI, urinary tract and heart.
- Blistering, ulceration of mucous membranes of urinary bladder. Oral, esophageal, and gastric hyperemia or ulceration and enterocolitis occur.
- Myocardial streaking, necrosis, and degeneration.
- Renal damage.

Diagnosis

- Clinical signs, lesions pre- and postmortem.
- Identification of beetle in hay.
- Recently developed (GC-MS) technique for identification of cantharidin in the urine, GI contents.
- Low serum calcium and magnesium.

Treatment

- No specific antidote.
- Remove animals from suspect feed.
- Activated charcoal + saline cathartic.
Fluid therapy in large volumes for shock, adjust for cardiac signs.
Bicarbonate (notable losses may occur due to salivation and shock).
Calcium gluconate and magnesium sulfate according to need.
Parenterally administered antibiotics may be indicated for ulcerative mucosal damage.

Black Blister Beetle and Striped Blister Beetle

Sulfonamides

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<th>Usual Duration (if survives)</th>
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<tr>
<td>Most species, esp. carnivores, poultry</td>
<td>Days to weeks</td>
<td>Days to permanent damage; potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

Sources

- Sulfonamides are bacteriostatic, white powders which are sparingly soluble in water but very soluble in alkaline and strong acid solutions. Sulfonamides are used in the therapy of bacterial infections or prophylactically in livestock rations.
- Also found in some anticoagulant rodenticide formulations to potentiate vitamin K1 inhibition.

Mechanisms of Action

- Antibacterial mechanism:
  - Sulfonamides are structural analogs of para-aminobenzoic acid (PABA) and competitively inhibit bacterial folic acid synthesis which utilizes PABA.
  - Sulfonamides cause crystalluria leading to nephrotoxicity.
    - Sulfonamides are less soluble in an acid urine than in alkaline urine, therefore, crystal formation is generally greater in the urine of carnivores as compared to herbivores.
    - Dosage and duration of therapy are obvious considerations, since increased concentration increases the probability of crystallization in the urine. Toxicsoses often result when the traditional dosage of 70 - 100 mg/lb of body weight is exceeded.
    - Administration of sulfonamides for longer than the customary course of 3 - 5 days may also increase the likelihood of poisoning.
• Dehydration due to decreased water intake or diarrhea for any reason increases the probability of toxicosis.

• Other mechanisms of toxicity:
  - Sulfonamides may sometimes interfere with iodine metabolism and therefore be goitrogenic.
  - Sulfonamides may cause agranulocytosis and thrombocytopenia.
  - Sulfonamides may have the potential to cause methemoglobin formation.
  - Sulfonamides may inhibit carbonic anhydrase and therefore can cause diuresis and acidosis.
  - Sulfonamides may cause arrested fetal development.
  - Sulfonamides may cause a peripheral neuritis in chickens, and cattle.
  - Sulfonamides may cause an acute drug shock. The mechanism responsible for this effect is unknown.
  - Sulfas may also cause acute anaphylactoid reactions, apparently due to a hypersensitivity (immune mediated) reaction.
  - Topical applications of sulfonamides may inhibit wound healing.
  - Sulfonamides may possibly interfere with ruminal flora B-vitamin production or enteric vitamin-K synthesis, although little data exists for the theories.
  - Some sulfonamides, such as sulfaquinoxaline may directly antagonize the action of vitamin K in the liver. Poultry and especially dogs may develop changes in clotting function. Dogs may exhibit increased one stage prothrombin time and increased activated partial thromboplastin time, and clotting time.
  - Because they are highly protein bound to plasma proteins, it may be possible for sulfonamides to displace anticoagulant rodenticides from albumin, making them more available to hepatocytes and hence more toxic.
  - Sulfamethazine has been implicated recently as a tumorigen by virtue of the occurrence of thyroid enlargements in laboratory animal studies. This and the presence of residues in the tissue of animals no longer being given these drugs in their feed intentionally has caused great consternation among regulatory agencies and may result in cessation of the use of this drug as a feed additive on many farms.

Absorption, Distribution, Metabolism and Excretion (ADME)

• Absorption-variable with type of sulfonamide administered. Some sulfas are rapidly absorbed from the GI tract, while others are poorly absorbed, "gut active" sulfas.
• Sulfonamides are metabolized to varying degrees, usually to conjugated or acetylated forms. Except for the pyrimidine sulfonamides, which include sulfamethazine, sulfamerazine and sulfadiazine, the acetylated forms readily pass through biological membranes, but are less soluble in the urine than the parent compounds.
• The different sulfonamides vary in toxicity in part as a result of their metabolism in the body. Sulfathiazole, for example, is highly excreted as the acetylated form and it is therefore more prone to cause toxicosis than most other sulfas.
• Sulfonamides undergo biliary and urinary excretion. They may also diffuse directly into the intestinal contents and undergo fecal excretion.
• Sulfonamides are excreted in the milk.
• Intruterine use results in detectable blood levels in cattle for at least 48 hours.
• For more information of particular compounds, see page 1089 of Veterinary Pharmacology and Therapeutics, 5th edition, Booth and McDonald, eds.; and pages 716 - 717 of the same book.

Clinical Syndromes

• Toxicoses are most frequent in dogs, cats, poultry and baby calves.
• Five types of syndromes are most likely to occur:
  1. Chronic or renal form.
  2. Acute drug shock, which may be allergic but the actual cause is not known.
  3. Hypersensitivity (anaphylactoid).
  4. Photosensitivity.
  5. Acute toxicosis.

1. **Chronic or Renal Form.**
   a. **Most important and common form of toxicosis** associated with sulfonamides.
   b. Signs may include:
      • Anorexia
      • Depression, collapse
      • Hematuria, albuminuria, and oliguria. Sulfonamide crystals may be present on preputial or vulvar hairs.
   c. **Additional signs in cattle** may include:
      • Transient agranulocytosis.
      • Mild hemolytic anemia.
      • Leukopenia.
      • Reduced milk production.
- Spinal and peripheral neuropathy.

d. **Additional signs in dogs** may be related to coagulopathy, although the greatest concern is when the sulfonamide is formulated with an anticoagulant rodenticide such as warfarin in order to potentiate its inhibition of vitamin K function. Keratoconjunctivitis sicca commonly occurs. Hepatopathy may develop.

e. **Additional signs in poultry** may include:
   - Poor egg production
   - Spinal and peripheral neuropathy
   - Poor growth

2. **Acute "drug shock".**
   a. **In calves** results from rapid IV administration.
      - Mydriasis
      - Ataxia
      - Blindness
      - Collapse
      - Possible death
   b. **In dogs** may occur after large parenteral or oral doses.
      - Emesis
      - Ataxia
      - Spastic paralysis
      - Epileptiform convulsions
      - Diarrhea

3. **Hypersensitivity.**
   a. Anaphylactoid reactions.
      - Occurs in horses and cattle.
      - Manifested as asthma or urticaria (hives).
      - Cross-reactions between sulfonamides may occur with animals reacting similarly to more than one member of the group.
   b. Drug allergy from trimethoprin-sulfadiazine.
      - Hypersensitivity reactions observed in Doberman Pinscher dogs. Clinical signs mimic immune-mediated disorder and include nonseptic polyarthritis, fever, polymyositis, anemia, and lymphadenopathy. Glomerulonephropathy, focal retinitis, leukopenia, and thrombocytopenia were also observed.
      - Reactions developed 10 - 21 days after the first drug exposure and/or within 1 hour to 10 days after reexposure.

4. **Photosensitivity.**
   - Sulfonamides infrequently cause photosensitivity. Skin rashes may result and these may be seen in conjunction with other effects such as hemolytic anemia and agranulocytosis.

5. **Acute toxicosis.**
   - Acute toxicosis from high doses of sulfonamides is rare.
   - Hypersalivation, vomiting, diarrhea.
   - Increased respiratory rate.
   - Weakness, ataxia, and spastic rigidity.

**Lesions**

- Few gross changes except for the presence in some animals of sulfonamide crystals in the renal pelvis and renal tubules. Kidneys may be gritty in texture when cut.
- Specimens of kidney tissue should be fixed in a slightly acidified formalin solution or in absolute ethanol to prevent dissolution of the crystals, which are readily observed microscopically in stained slides, especially with polarized light.
- Bone marrow depression may sometimes be seen.
- Hemorrhagic diathesis may be seen in birds receiving sulfaquinoxaline.
- In photosensitivity, appropriate skin lesions may be seen.
- Secondary effects of uremia may be noted in the renal form.
Diagnosis

- Appropriate history of exposure and lesions are very important in the diagnosis.
- Chemical confirmation is important in many cases and appropriate specimens, depending upon the likely source, may include:
  - Feed
  - Premix
  - Water
- Note: With some methods of analysis, arsanilic acid and procaine penicillin may give false-positives.
- Concentrations of a sulfonamide in muscle, kidney, or liver above 20 ppm substantiate a diagnosis.
- In hypersensitivity, a history of previous exposure to sulfonamides and appropriate clinical signs warrants a tentative diagnosis.
- In anaphylactoid reactions, very recent initial exposure and appropriate clinical signs warrant a tentative diagnosis.

Treatments

- Terminate exposure. In the rare case of acute overdose, judicious efforts should be undertaken to evacuate the gastrointestinal tract, using an emetic, lavage, saline cathartic, and/or adsorbent as indicated by the dosage, time factors, and species involved.
- Obviously removal of sources in the feed and water must also be accomplished.
- The half-life of sulfonamides can be decreased by the administration of fluids and by increasing the urine pH. Fluid therapy may therefore be indicated and alkalization of the urine is recommended using bicarbonate either in the fluids or orally. Fluid therapy must be monitored to prevent overhydration in anuric animals.
- Vitamin K₁ is indicated in cases of hypoprothrombinemia or concurrent exposure to a coumarin or indandione anticoagulant.
- Acute anaphylactoid reactions may be treated with epinephrine.
- Hypersensitivity reactions may be treated with antihistamines if needed.
- When possible, other drugs which are protein bound should not be used in animals already carrying toxic concentrations of sulfonamides on board since the sulfas may be displaced from the albumin, diffuse into tissues or be filtered by the kidney resulting in increased toxic effects.

Amphotericin-B

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<td>Most species</td>
<td>Days to weeks</td>
<td>Few days to permanent damage; potentially lethal</td>
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Sources

- Amphotericin-B (Fungizone) is a polyene antibiotic used in the treatment of various systemic mycotic infections such as:
  - Coccidioidomycosis.
  - Histoplasmosis.
  - Candidiasis.
  - Blastomycosis.
  - Aspergillosis.
- The drug is prepared for IV injection.
Toxicity

- Amphotericin-B is nephrotoxic at recommended dosage rates and renal toxicity is expected in most courses of therapy at some point.
- Reversible renal dysfunction develops in more than 80% of human patients receiving amphotericin-B. The same renal dysfunction routinely occurs in veterinary patients as well.
- For this reason, the drug is often used every other day or in courses of one week on, one week off, etc.
- Generally, the blood urea nitrogen is monitored before and during the course of therapy and treatment is continued as long as the BUN remains below 40 mg%.
- Such infections are often treated for 6 - 8 weeks.

Mechanism of Action

- Poor oral absorption, therefore given intravenously. Persists in blood for 18 - 24 hours at comparatively high concentrations.
- Amphotericin-B interacts with sterols of cell membranes forming pores or channels which leak various small molecules (see mention of chloride below), thereby disrupting cellular compartmentalization of the cell from the outside (intracellular) environment.
- Most of the adverse effects of amphotericin are probably related to disruption of the mammalian cell membrane.
- Nephrotoxicity may be related to a decrease in intrarenal blood flow associated with arteriolar vasoconstriction, a subsequent decrease in GFR, and impaired tubular function.
- Nephrotoxicity may be explained further on the basis of a tubuloglomerular feedback mechanism. Amphotericin causes an increase in permeability to chloride ions, causing excess chloride to be presented to the distal tubule. A tubuloglomerular feedback response causes a compensatory decrease in GFR and renal blood flow to occur. Excessive response has the potential to cause ischemia.
- Amphotericin-B has also been reported, in man and rats, to cause renal tubular acidosis.
- Defects of urine concentrating ability occurs in dogs and man. May reduce response to antidiuretic hormone (ADH).
- Low erythropoietin production during therapy may result in anemia.

Pathophysiology associated with amphotericin B nephrotoxicity - Amphotericin acts on several sites of the nephron. At site 1 there is vasoconstriction, either as the result of direct action of the drug on the vessels or by reflex mechanisms. This results in decreased renal blood flow and azotemia; it may increase renal damage by causing renal ischemia. At site 2 the membranes of the distal tubule cells show altered
permeability. This may initiate reflex mechanisms to decrease GFR (by tubuloglomerular feedback) and may cause excessive loss of electrolytes, producing hypokalemia and distal renal tubular acidosis. At site 3 the action of ADH is antagonized, which produces defects in urine concentration. *(Figure from Current Veterinary Therapy IX, Small Animal Practice)*

**Signs**

- Fever.
- Nausea, vomiting, and diarrhea.
- Anorexia and weight loss.
- Polyuria, oliguria, or anuria.
- Increased numbers of casts in the urine sediment (granular or cellular).
- Hematuria or proteinuria.
- Anemia.

**Treatment**

- Maintaining good hydration is essential in prevention of clinical toxicosis in the first place.
- Therapy is largely directed at supporting renal function and assisting detoxification of nitrogenous byproducts as in other forms of kidney failure.
- Fluids are indicated and the concomitant use of mannitol with amphotericin-B has been found to reduce its nephrotoxicity in dogs. Sodium loading decreases amphotericin toxicity.
- Monitor PCV, total protein, BUN, and serum creatinine. Therapy should be discontinued if BUN becomes abnormal or if severe systemic toxic signs appear such as depression or vomiting.
- If hypokalemia develops, potassium supplementation should be instituted.

**Other Nephrotoxic Antibacterial Agents**

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**Introduction**

The kidney is exceptionally vulnerable to toxicants. Renal blood flow accounts for 20% of cardiac output, with 90% of this going to the renal cortex. The kidney also consumes oxygen at an extraordinary rate, making it quite sensitive to cellular hypoxia. The countercurrent mechanism of the kidney also predisposes the medullary interstitium to toxicity because of the progressively increasing tissue concentrations of nephrotoxic agents.

**Sources**

- Antibacterials: aminoglycosides, cephalosporins, isoniazid, penicillins, sulfonamides (see separate section), tetracyclines.
- Antifungals: amphotericin-B.
- Anthelmintics: arsenicals, thiacetarsamide.
- Analgesics: NSAID, acetaminophen, ibuprofen, phenylbutazone, salicylates.
- Bacitracin:
  - Strongly nephrotoxic when given parenterally, therefore not given by this route. Not absorbed orally, so can be used for gastrointestinal infections. Also widely used topically.
- Polymyxin-B:
  - Not absorbed from the skin or intestine but sometimes used by injection.
  - Occasional toxicosis, primarily affecting renal and otic function results from parenteral administration. Dogs are especially sensitive.
- Tetracyclines:
  - The use of tetracyclines can result in progressive azotemia due to antianabolic effects of these drugs. Uremia is more pronounced in animals with preexisting renal disease.
- Oxytetracycline:
  - One report in calves.
Cephalosporins:
- Cephaloridine is the most nephrotoxic of all available cephalosporins.
- Occasionally reported as a cause of acute renal failure in dogs and cats.
- Inhibits renal cation transport, which may lead to an increase in drug concentration within the renal cortex.
- Cephaloridine depletes cortical glutathione which leads to membrane lipid peroxidation and necrosis.

Penicillins:
- Not directly nephrotoxic. Nephrotoxicity dependent upon immune-mediated hypersensitivity.

Aminoglycoside antibiotics:
- Aminoglycosides have a low therapeutic index and renal dysfunction may occur in 10 - 20% of all courses of therapy.
- Aminoglycosides include gentamicin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin.
- All aminoglycosides are nephrotoxic and ototoxic. Each has an ability to damage renal proximal tubules. Neomycin is considered the most nephrotoxic aminoglycoside. The other nephrotoxic aminoglycosides in decreasing order of toxic potential are: gentamicin, tobramycin, amikacin, and streptomycin.
- Mechanisms.
  - Aminoglycosides are eliminated by glomerular filtration. Proximal tubules of the kidney actively uptake aminoglycosides. Continued use increases the likelihood of nephrotoxicity.
  - Risk factors that predispose a patient to nephrotoxicity include prolonged therapy, preexisting renal disease, advanced age, dehydration, concomitant exposure to other nephrotoxic agents, and diuretic (especially furosimide) use.
  - Exact cellular mechanisms of nephrotoxicity are unknown but may include inhibition of protein synthesis, inhibition of phospholipases, altered mitochondrial action, and inhibition of Na-K ATPase function.

Neomycin:
- Poorly absorbed after oral or topical administration.

Gentamicin:
- Widely used for systemic bacterial infections and for urinary infections in spite of its nephrotoxic properties. Renal function should be closely monitored in vigorously treated patients and in all patients on extended courses of therapy. In the presence of renal disease or urinary obstruction, other drugs should be selected whenever possible.
- Clinical signs of nephrotoxicity are referable to acute tubular necrosis and acute renal failure.
- Gentamicin nephrotoxicity follows 4 stages including: 1) functional changes (polyuria, proteinuria, glucosuria), 2) proximal renal tubular cell death (casts), 3) decreased GFR (azotemia), and 4) regeneration when cell necrosis is complete.
- Treatment-Nephrotoxicosis due to aminoglycosides is usually reversible. Discontinue use of the offending drug. Avoid the use of loop diuretics. Institute fluid therapy (and hemodialysis if necessary) as for other causes of acute renal failure.

### Carbamate Fungicides

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Sources

Carbamate fungicides such as Maneb and Zineb are widely used in orchards and garden and agricultural applications.

Toxicity

- Very low in toxicity. Rat oral median lethal doses:
  - Zineb LD₅₀ was > 5,200 mg/kg.
  - Maneb LD₅₀ was 7,990 mg/kg.

Effects

Nephrotoxic and hepatotoxic but only at massive exposure rates.

Comments

The primary reason to mention these compounds is that it is important to avoid confusion of these compounds with the carbamate insecticides, some of which are extremely toxic inhibitors of acetylcholinesterase.
Analgesic Nephropathy

I. Introduction

Analgesic nephropathy was first described in 1953 in human patients as the result of prolonged consumption of combination analgesics containing phenacetin, aminopyrine, caffeine, isopropylantipherine, and persedon [1]. Since that time, the development of papillary necrosis has become recognized as a characteristic pathologic finding in the classic syndrome [1]. Clinically, analgesic nephropathy is characterized in humans by the development of proteinuria, decreased glomerular filtration rate (GFR), hematuria, anemia, and flank pain. In addition to papillary necrosis, a number of renal syndromes have become associated with the consumption of nonsteroidal anti-inflammatory drugs in both animals and humans [2-4].

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a wide range of pharmacologically active agents with diverse chemical structures. Chemical classes of NSAIDs include: a) salicyclic acid derivatives (e.g., aspirin), b) phenylacetic acids (e.g., diclofenac), c) heterocyclic acetic acids (e.g., indomethacin, sulindac), d) proprionic acids (e.g., ibuprofen, naproxen), e) fenamic acids (e.g., flufenamic), f) pyrazolones (e.g., phenylbutazone), and g) oxicams (e.g., piroxicam). Among all NSAIDs, the common mechanism of action for their anti-inflammatory properties resides in their ability to inhibit cyclooxygenase, an enzyme required for prostaglandin synthesis.

II. Review of Prostaglandin Effects on the Kidney

A. Prostaglandin synthesis

Prostaglandins (PGs) are unsaturated fatty acids which are derived from 20-carbon essential fatty acids, of which the most important is arachidonic acid. Arachidonic acid is released from damaged cell membranes and is metabolized by either cyclooxygenase, which leads to PG formation, or lipoxygenases, which results in leukotriene synthesis. The biological activity of most PGs is exerted primarily at the local site of synthesis due to their short circulatory half-life.

In the kidney, the major vasodilatory prostaglandins are PGE2 and PGI2 (prostacyclin), the production of which is stimulated by vasoconstrictive substances including angiotensin II, norepinephrine, and antidiuretic hormone. The major physiologic role for vasodilatory PGs is to modulate the pressor effects of vasoactive substances on the kidney and maintain adequate renal blood flow (RBF) and GFR. The modulating action of PGs plays a minimal role in controlling renal function in healthy euvolemic individuals, but during certain pathophysiologic states, vasodilatory PG production is required to maintain adequate renal perfusion and function.

Renal prostaglandin synthesis is compartmentalized; for example, microsomes isolated from cortical as well as medullary portions of the kidney are capable of producing PGD2, PGE2, PGF2, PGI2, and TxA2 in varying amounts. In general, the bulk of PG synthetic capacity is located in the medulla [6]. The location of PG degradative enzymes within the kidney is not as well delineated (versus sites of biosynthesis). Considerable spontaneous hydrolysis is likely.

B. Physiologic actions of prostaglandins

1. Renal blood flow - Studies in the dog show that PGE2, PGD2, and PGI2 reduce total renal resistance and increase renal blood flow, whereas PGF2 and 6-keto PGF1 (hydrolysis product of prostacyclin) exert little or no effect [7-9]. Prostaglandins also influence the intrarenal distribution of blood flow; for example, intrarenal infusion of arachidonic acid in the dog results in greater increases in inner cortical blood flow than in the outer [10]. Conversely, the NSAID indomethacin shifts cortical blood flow to superficial regions, decreases medullary blood flow, and reduces blood flow rate in papillary vasa recta capillaries.

In the conscious dog or baboon, inhibition of PG synthesis has little or no effect on renal blood flow [11]. The experimental use of cyclooxygenase inhibitors provides supportive evidence for the role of PGs in attenuating the renal vasoconstrictive influences of angiotensin II, norepinephrine, and alpha-adrenergic neural stimulation. Although PGs modulate the effects of vasoconstrictors on the renal microcirculation, there is little evidence that these compounds play a role in autoregulation. For

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Nephrotoxic Organic Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Small animals, horses</td>
<td>Hours to days</td>
<td>Days to permanent damage; often lethal</td>
<td>Non-steroidal Anti-Inflammatory Agents</td>
</tr>
</tbody>
</table>
III. Clinical (Renal) Syndromes Associated with NSAIDs

Several types of acute renal dysfunction have been associated with the use of NSAIDs, the most common being: acute renal failure, hyperkalemia, and acute interstitial nephritis with or without proteinuria (Table 1). The most commonly encountered adverse renal effect related to the use of NSAIDs is prostaglandin-dependent renal insufficiency [3,17].

A. Acute renal failure
Prostaglandin-mediated acute renal failure is characterized by oliguria, azotemia, and occasionally hyperkalemia. In general, NSAID-mediated acute renal insufficiency is reversible, and discontinuation of NSAID therapy results in a return to basal renal function.

Phenylbutazone has been implicated in the horse in the development of acute renal failure; renal medullary crest necrosis; and oral, gastric, duodenal, and colonic ulcers [18,19]. In addition, uremia and gastrointestinal ulceration have also been described in dogs following the ingestion of ibuprofen [20] and naproxen [21]. Acute renal failure as a result of decreased production of vasodilatory prostaglandins (PGE2 and PGI2) most commonly occurs when systemic vasoconstrictive influences are present (Table 2). Water deprivation has been demonstrated to be a potential risk factor which predisposes horses to the development of phenylbutazone nephropathy [22]. The appearance of analgesic nephropathy and papillary necrosis are thought to be the result of an ischemic process and endothelial necrosis. The development of renal medullary ischemia is considered to be the initiating factor in the production of papillary necrosis. The apparent predisposition for the development of lesions at the papillary tip is believed to be the result of higher relative concentrations of drug and metabolites in this region of the kidney, as well as the relatively poor blood supply to the renal papilla when compared to the rest of the medulla. Experimental NSAID administration to anesthetized animals has revealed medullary ischemia as a result of shunting of blood flow from the renal medulla to the cortex [23].

In human patients, a syndrome of acute oligoanuric renal failure has also been associated with phenylbutazone use. One proposed mechanism for the development of "phenylbutazone anuria" in human patients is a phenylbutazone-mediated inhibition of uric acid reabsorption which results in hyperuricosururia, uric acid urolithiasis, and bilateral ureteral obstruction [24]. Irreversible renal injury in the form of papillary necrosis has also been associated with ibuprofen, fenoprofen, and mefenamic acid therapy in human patients.

B. Hyperkalemia
Prostaglandins mediate the release of renin in response to changes in blood pressure and sodium delivery to the macula densa. Prostaglandins may also stimulate aldosterone production through influences on renin release. Decreased renal prostaglandin synthesis as a consequence of NSAID use in humans has been implicated as a cause of hyporeninemic hypoaldosteronism [25]. The treatment of hyporeninemic hypoaldosteronism with furosemide (administration stimulates renal prostaglandin release) provides additional supportive evidence for the role of PGs in renin release. Decreased plasma renin activity has been reported in man for virtually all NSAIDs with the possible exception of sulindac. The persistence of hypoaldosteronism in the presence of marked hyperkalemia is further supportive evidence that potassium-mediated secretion of aldosterone by the adrenal cortex is also suppressed. In addition,
hyperkalemia may be a result of a PG-induced defect in cellular uptake of potassium [11].

C. Interstitial nephritis [2,3]
There have been case reports involving human patients who developed a syndrome of acute renal failure with proteinuria following NSAID administration. Onset generally occurs from 2 weeks to 18 months after the initiation of NSAID therapy. Steroids have been used to accelerate recovery, although their efficacy remain unproven. Microscopic examination of the urine sediment frequently reveals evidence of hematuria and pyuria. The combination of an "active" urine sediment and proteinuria in the absence of prior renal compromise helps differentiate this syndrome from other forms of NSAID-related acute renal failure. Histologic examination demonstrates normal renal glomeruli, focal diffuse interstitial infiltrates consisting primarily of lymphocytes, and vacuolar degeneration of the proximal and distal tubules. In general, the glomeruli are minimally altered with extensive fusion of epithelial-foot processes occasionally noted.

This syndrome has been reported in human patients taking fenoprofen, naproxen, tolmetin, sulindac, and indomethacin. Despite its idiosyncratic nature, the syndrome is produced by at least 2 structurally distinct NSAID classes (phenylpropionic acid and indoacetic acid derivatives) which may represent a common metabolic pathway. It has been proposed that interstitial nephritis may be the result of T cell activation and secondary autoimmune-mediated damage. Inhibition of cyclooxygenase by NSAIDs may also lead to shunting of arachidonic acid precursors into the lipooxygenase pathway, which would favor production of lymphokine-like inflammation-inducing metabolites of eicosatetraenoic acid.

IV. Clinical Management

See Nonsteroidal Anti-Inflammatory Agents for important information on management of animals with NSAID overdose.

A. Analgesic nephropathy
In general, acute renal insufficiency resulting from prior NSAID administration has been considered reversible. Dopamine has sometimes been recommended for the treatment of human patients with NSAID-induced interstitial nephritis. In general, the development of papillary necrosis (as a result of NSAID use) is considered an irreversible condition. It should be noted, however, that renal papillary necrosis has been considered to be an incidental finding in some horses treated with phenylbutazone and may not necessarily result in compromised renal function [27]. The use of synthetic PGE2 has been examined for possible benefits in the prevention of phenylbutazone toxicoses in ponies. The administration of synthetic PGE2 (before and after the daily administration of phenylbutazone) in these animals resulted in a reduction in the formation of gastrointestinal ulceration and hypoproteinemia [28]. Prostaglandin E analogs, such as Misoprostil® are now recommended for animals with acute analgesic nephropathy.

B. Acute NSAID overdose
The most commonly encountered situation in small animal toxicology is the massive, acute ingestion of NSAID-containing medications. Management of acute NSAID poisoning is essentially symptomatic and supportive. In recent ingestions, the oral administration of single or repeated doses of activated charcoal will reduce the absorption of most NSAIDs [29]. The use of dopamine and/or dobutamine may increase renal perfusion and minimize the degree of renal insufficiency. Occasionally, animals may develop seizures following the ingestion of large quantities of NSAID, and the use of diazepam to abolish seizure activity is indicated. The most prevalent adverse side effect encountered as a result of NSAID ingestion is the development of gastrointestinal irritation and ulceration. The use of sucralfate and cimetidine has been recommended for the treatment of NSAID-induced gastric ulceration.

V. Conclusions

Analgesic nephropathy is primarily an extension of the pharmacologic action of these agents (inhibition of prostaglandin production by the kidney). In the kidney, PGE2 and PGI2 primarily function as vasodilatory agents, and during certain disease states (e.g., congestive heart failure, water depletion), the production is required for compensatory renal autoregulatory mechanisms. Historically, it has been during these disease states that analgesic nephropathy most commonly occurs. The inhibition of prostaglandin synthesis by NSAIDs can also predispose some individuals to the development of interstitial nephritis, electrolyte imbalances (e.g., hyperkalemia), and water retention. Areas of apparent ongoing research efforts and controversy include:

A. The localization and extent of prostaglandin synthesis within the kidney. In addition, characterization of the types, amounts, and physiologic activity of prostaglandins produced by renal tissues. Future effort into the delineation of the compartmentalization of prostaglandin degradative enzymes within the kidney is also needed. Research efforts into these areas have been hampered by the use of in vitro tissue culture techniques which minimize renal blood and tubule fluid dynamics and the lack of sensitive chemical assays for the presence or absence of prostaglandins and associated enzymes.

B. Determination of the correlations between observed renal toxicity and the urinary excretion of prostaglandins. Measurements of urinary prostaglandins and correlation to renal cyclooxygenase activity have been hampered because of the concurrent production of potentially cross-reacting metabolites, namely some of the prostaglandins and thromboxane.
C. Studies into the prevalence of and risk factors for the development of analgesic nephropathy and NSAID-induced renal insufficiency in companion animals are needed. As the population of geriatric animals increases, a growing number of animals are likely to receive NSAIDs. In addition, characterization of the renal syndrome(s) produced by chronic use of NSAIDs in companion animals is needed. Of additional concern is the need to identify likely threshold doses for the development of renal insufficiency in acute NSAID overdose in companion animals.

D. Further studies into the pathophysiologic mechanisms which underlie the development of papillary necrosis, interstitial nephritis (e.g., the role of humoral response), and electrolyte imbalance is also needed. Similarly, studies into potential therapeutic regimens for the treatment of analgesic nephropathy are needed (e.g., the efficacy of steroids in interstitial nephritis, potential use of synthetic prostaglandins in preventing or modifying toxicity).

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### Table 1 - Clinical syndromes of nephrotoxicity with NSAIDs.

<table>
<thead>
<tr>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Renal insufficiency: Prostaglandin synthesis of nephrotoxicity with NSAID-enhanced renal vasoconstriction often in the context of diminished basal renal blood flow.</td>
</tr>
<tr>
<td>2. Hyperkalemia: Prostaglandin synthesis inhibition leads to hyporeninemic hypoaldosteronism and resultant hyperkalemia.</td>
</tr>
<tr>
<td>3. Interstitial nephritis: Direct nephrotoxicity, often results in heavy proteinuria.</td>
</tr>
<tr>
<td>4. Sodium and water retention: Diuretic resistance possibly due to aldosterone-like effect of NSAIDs as well as antinatriuretic effect of PG synthesis inhibition; water retention in part secondary to PG synthesis inhibition and enhanced effect of vasopressin.</td>
</tr>
<tr>
<td>5. Anaphylaxis</td>
</tr>
</tbody>
</table>

### Table 2 - Clinical and experimental conditions in which renal function is prostaglandin dependent.

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low renal perfusion pressure by hemorrhagic hypotension.</td>
</tr>
<tr>
<td>2. Extracellular volume depletion of diuretics.</td>
</tr>
<tr>
<td>3. Anesthesia and surgical stress.</td>
</tr>
<tr>
<td>4. Reduced cardiac output.</td>
</tr>
<tr>
<td>5. Renal disease including nephrotic syndrome or chronic glomerulonephritis.</td>
</tr>
<tr>
<td>6. Hepatic cirrhosis (ascites).</td>
</tr>
</tbody>
</table>

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### Other Agents Causing Nephrotoxicoses and Oxalate Excretion

<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>Ethylene glycol (See Toxicants that Cause Acidosis)</td>
<td>Mostly dogs</td>
<td>Minutes to hours</td>
<td>Few days to permanent damage; often lethal but toxicosis is rare</td>
</tr>
</tbody>
</table>

**Ethylene Glycol**

As mentioned under agents causing acidosis, ethylene glycol toxicosis causes a nephrosis characterized by dilated tubules with damage to tubular epithelial cells, deposition of calcium oxalate crystals, and both oxalate and hippurate crystaluria. Renal failure may result in an acute illness after the animal has survived the acidosis stage or, after repeated ingestions, may be the principle problem first encountered. Usually, if the animal survives an acute toxicosis, the renal effects of ethylene glycol resolve with time; however, in some cases chronic renal failure results.
Oxalic Acid -

Oxalic acid is available in crystalline form over-the-counter and people use it for rust removal from various surfaces and from fabrics. Although rarely encountered by domestic animals, this can be a potent toxicant causing serious or lethal toxicosis. Anticipated effects include gastrointestinal irritation, oxalate crystalluria and oxalate nephrosis and possibly acute hypocalcemia and death.

Rumex -

A genus of oxalate containing plants not mentioned in the subsequent section of these notes is *Rumex* spp., also known as curly dock, sour dock, or sheep sorrel.

Images

- Curly Dock, *Rumex crispus*. Source: Cornell University, Poisonous Plants Informational Database (www.anisci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -
- Curly Dock, *Rumex crispus* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

Curly Dock, *Rumex crispus* L. 1, lower part of plant; 2, upper part of plant; 3, seed; 4, distribution. **Perennial**, with large, yellow, somewhat branched taproot, reproducing by seed. **Stems** smooth, erect, 1 to 4 feet (0.3 to 1.2 m) tall, single or in groups from the root crown.
Cholecalciferol-Based Rodenticides and Other Vitamin D-Containing Products.
Multiple Vitamin Preparations

Sources

- Cholecalciferol (Vitamin D3)-containing rodenticides are marketed as, among others, Quintox® (Bell Laboratories), Rampage, Ortho Rat-B-Gone, and Ortho Mouse-B-Gone® brand names. Marketed as an acute single feeding or chronic (multiple feeding) rodenticide.
- Quintox® is available in 2 bait forms: a mouse seed (sold as 10 gram place pac) and a cereal rat and mouse bait (sold as 30 gram pouch). The Ortho products are available in a box that contains four 40-gram packs.
- Muritan® is also listed as a rodenticide source of cholecalciferol in the book, Farm Chemicals '96.
- Cholecalciferol is present at 0.075% concentration in final bait formulations. Cholecalciferol naturally exists in animals as a precursor of active vitamin D. Its intrinsic biological activity, however, is low.
- Advertised as having no bait shyness, and reported effective against anticoagulant-resistant rodents. Rodent deaths delayed 2 - 5 days. After lethal dose is consumed all feeding stops.
- Cod liver oil is another source of Vitamin D as well as Vitamin A.
- See also Vitamin D containing plants (next section).
- Vitamin D2 (ergocalciferol) is the plant form of Vitamin D. It is not utilized by poultry and only poorly utilized by swine.)
- Calcipotriene (Dovonex® ointment and less often lotion) used for humans with psoriasis has repeatedly poisoned dogs.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D3 (especially cholecalciferol rodenticides)</td>
<td>Dogs, other pet animals</td>
<td>24 - 72 hours</td>
<td>Weeks to permanent damage; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Toxicity

- Based upon clinical reports, toxicoses have occurred in dogs from the ingestion of cholecalciferol at 0.5 - 3 mg/kg body weight. Administration of 10 - 20 mg/kg to dogs of cholecalciferol-based rodenticide resulted in death in 4 dogs.
- Younger animals appear at higher risk to the development of toxicosis.
- Acute oral LD50 in dogs of technical material in oil has been reported to be 85 mg/kg. This has lead to an underestimate of the actual hazard of the rodenticide products for this species.
- Relay toxicosis: not reported in experimental studies.
- 40 IU vitamin D = 1 mcg. Thus, 1 IU of vitamin D3 = 0.025 mcg of cholecalciferol.

Mechanism of Action

- Calcium homeostasis is under the control of: 1) parathyroid hormone (PTH), 2) calcitonin, and 3) vitamin D metabolites. Calcium concentration of the blood is composed of "diffusible calcium" including the citrate bound and free calcium ion (ionic calcium).
Clinical Signs

- Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid gland. Parathyroid hormone feedback system is relatively simple, controlled primarily by serum calcium ion concentration (magnesium ion has lesser effects). As serum calcium levels rise, PTH levels decline. Parathyroid hormone has its primary effects on the bone, kidney, and to a lesser degree the intestine. PTH acts on bone to mobilize calcium (from skeletal reserves) into the extracellular fluid (increased osteoclastic and osteocytic activity. Prolonged PTH levels result in increased osteoclast numbers). PTH exerts a rapid effect on the proximal renal tubules resulting in decreased phosphate reabsorption. PTH also enhances distal convoluted tubule reabsorption of calcium. Finally, increased intestinal absorption of calcium occurs as a result of PTH influence.
- Calcitonin (CT) is secreted by thyroid parafollicular (C) cells. PTH and CT have antagonistic effects on bone reabsorption, but synergistic effects on renal tubular reabsorption of phosphorous. Blockade of osteoclastic and osteocytic bone reabsorption occurs as a result of calcitonin activity.
- Cholecalciferol (vitamin D3) is synthesized in the epidermis under the influence of sunlight from its precursor, 7-dehydrocholesterol. Vitamin D binding protein transports cholecalciferol from the skin into the blood. Vitamin D3 from dietary sources is absorbed by facilitated diffusion and becomes bound to alpha-2-globulin in blood. Cholecalciferol is then enzymatically (calciferol-25-hydroxylase) converted to 25,hydroxycholecalciferol (25-OH-D3) in the liver. Then 25-OH-D3 is transported to the kidney, where further metabolism (by 25-OH-D3-1 hydroxylase) to 1,25 dihydroxycholecalciferol (1,25-(OH)2-D3) occurs. The conversion of 25-OH-D3 to 1,25-(OH)2-D3 is rate-limiting, and partially explains the delay in biological activity of dietary vitamin D3.
- In the liver, 1,25-(OH)2-D3 can also be converted by 24-hydroxylase to 24,25 dihydroxycholecalciferol (24,25-(OH)2-D3). The 24,25-(OH)2-D3 is less active and is preferentially formed when high serum calcium levels exist. Vitamin D metabolites increase serum calcium concentration in the following ways:
  1. Vitamin D and its active metabolites function to increase the absorption of calcium and phosphorus from the intestines. The major target tissue for 1,25-(OH)2-D3 is the small intestine where it increases the active transcellular transport of calcium and phosphorus.
  2. The absorptive capacity of the intestine for calcium is a direct function of the amount of calcium binding protein (CaBP) present. Synthesis of CaBP is stimulated by vitamin D metabolites.
  3. The active metabolites of cholecalciferol also act on bone. Vitamin D (in the presence of PTH) is required for osteoclastic resorption and calcium mobilization from bone. Cholecalciferol, 25-OH-D3 and 1,25-(OH)2-D3 stimulate osteoclastic proliferation and resorption of bone. On a per weight basis 1,25-(OH)2-D3 is 100 times more potent in stimulating bone resorption than is 25-OH-D3.
- Active metabolites of vitamin D also stimulate the retention of calcium by increasing its renal distal tubular reabsorption.

Clinical Pathology

- The most profound alteration in serum chemistry is an elevated serum calcium (more than 11.5 mg/dl in adult). Elevations in serum phosphorous occurred at 12 hours postingestion and preceded serum calcium rise (occurred 24 hours postingestion). Increased BUN and creatinine are also seen.
- Urine specific gravity may be in the hypostenuric range (1.002 - 1.006). Proteinuria and glycosuria may be seen.
- **Note** - Adjusted calcium values (adjusted for protein binding by albumin) may need to be considered. Corrected calcium = Ca (mg/dl) - albumin (gm/dl) + 3.5. Alternatively, ionized calcium concentrations can be determined directly by many laboratories.
- Condition must be distinguished from normally occurring (physiologic) juvenile hypercalcemia; therefore, a baseline serum calcium determination is generally indicated as soon after ingestion as possible.
Lesions

- Morphological changes seen in dogs given vitamin D experimentally included: roughened, red, raised plaques in aorta or pulmonary artery. Histopathologically, these were characterized by intimal proliferation, subintimal edema, and hemosiderin deposition. Thyroid glands were grossly enlarged and paler than normal, microscopic changes included hypertrophy and hyperplasia of parafollicular (C) cells.
- Lesions associated with renal involvement included kidneys with red and gray cortical surfaces. Calcium deposition was random. Degeneration of renal tubular epithelium was evident microscopically. Mild glomerular degeneration was observed. Mineralization occurred in the basement membrane of tubules, especially the ascending loop of Henle, collecting and distal convoluted tubules occurs. This can be a critical problem since renal tubular epithelium regeneration requires an intact basement membrane.
- Calcification and necrosis of intramural coronary arteries, gastric mucosa, intestinal wall, parietal pleura, terminal pulmonary airways, thyroid, pancreas, and urinary bladder was observed. Myocardial degeneration, necrosis, and mineralization may occur.

Diagnosis

- Based upon exposure history, clinical signs, development of hypercalcemia, and if death occurs, lesions. Differential diagnoses include hypercalcemia secondary to paraneoplastic syndrome (most commonly observed with lymphosarcoma), juvenile hypercalcemia, and hyperparathyroidism.
- Kidney calcium concentration may be in the range of 1,000 parts per million as compared to approximately 100 parts per million for controls.

Treatment for Animals Exposed to Cholecalciferol Rodenticides

- Current recommendations for the control of hypercalcemia are as follows (treatment should be followed in order):
  - If patient has recently (< 3 hours) consumed cholecalciferol bait, emesis should be induced.
  - Activated charcoal and a saline cathartic are administered depending upon the likelihood of the presence of unabsorbed bait in the digestive tract. Also, repeated doing may be of value in counteracting enterohepatic recirculation of vitamin D and its active metabolites.
  - Determine baseline serum calcium levels as soon as the animal is presented if a potentially toxic dose was digested. Continue monitoring serum calcium levels approximately every 24 hours to determine if further therapy is required. If therapy is required, it is continued until, when it is withdrawn, serum calcium levels are found to remain normal.
  - Fluid therapy consists of IV normal saline and furosemide (5 mg/kg given IV followed by 2.5 - 4.5 mg/kg TID to QID per os) as a diuretic. Thiazide diuretics should not be used because they decrease urinary excretion of calcium and may contribute to or cause hypercalcemia. Saline is preferred over other fluids, because of enhancement of calcium elimination in the urine.
  - Patient should be placed on a low calcium diet (such as s/d, u/d/, or k/d), and sunlight should be avoided.
  - Cortisone should be administered (2 - 3 mg/kg). Corticosteroids have several beneficial effects including inhibition of osteoclast-activating factors (OAF) action on bone. In addition, cortisone directly inhibits release of OAF and depresses PG 2 mediated release of OAF. Corticosteroids also exert a hypercalcicuric effect and cause decreased intestinal absorption of calcium.
  - Calcitonin (salmon calcitonin) has been used in the treatment of hypercalcemia. This is to be given in microgram quantities (4 - 6 IU/kg) SQ every 2 - 3 hours initially until serum calcium levels stabilize. Therapy should be individualized according to need. Long-term calcitonin administration (weeks) at increased doses may be required. Foreign protein reactions are possible necessitating therapeutic administration of epinephrine and possibly other agents as well as discontinuation of further use of calcitonin.
  - Pamidronate (Aredia®), a second generation biphosphonate, blocks dissolution of hydroxyapatite and decreases conversion of calcifidiol to calcitriol. It has a long half life in vivo. It can be used instead of calcitonin. Although very expensive, e.g., $300 for one dose for a 25 kg dog, only one to a few treatments may be needed.
  - Treatment with diuretics and corticosteroids should continue until the animal's serum calcium concentrations have stabilized in the normal range. Often treatment should continue for 2 weeks, followed by removal of therapy, and retesting of serum calcium levels after 24 hours. Continue 1-week-long regimens of diuretic/corticosteroid until serum calcium remains normal after their withdrawal (check serum Ca++ at 24, 48, and 72 hours after final therapy). Monitor serum calciums and BUN as needed throughout therapy.

Case Report

- On 3/4/86, a 3 month old female Rottweiler (12 lb, 5.4 kg) was thought to have eaten approximately 15 grams of Quintox (1/2 packet). On the next day, 3/5/86, the animal was lethargic, vomiting, and had a temperature of 102.5 °F. The dog was started on IV normal saline and penicillin. WBC = 15,000, PCV = 32, TP = 5.6. On 3/7/86, the dog was depressed, vomiting, had a painful abdomen and difficulty breathing. Urine sp gr = 1.010, BUN too elevated to determine, calcium (uncorrected) = 13.6, WBC = 12,000, PCV = 33, and TP = 5.6. Treatment was changed to normal saline with potassium and bicarbonate IV. IV dexamethasone (Azium ) was also administered. Deterioration of the dog's condition continued until 3/10/86 when the owners elected euthanasia. Histopathology revealed tubular degeneration and mineralization of the renal tubules, mineralization of alveolar septa, and focal parenchymal hemorrhage in the lung.
- Total kidney concentrations elevated (300 - 1,000 ppm on wet weigh basis).
- Serum concentrations of cholecalciferol and/or its metabolites may be supportive.

---

### Vitamin D (and Multivitamin Preparations)

**Sources**

- **Note** - Vitamin D, 40 IU = 1 mcg.
- Many multivitamin preparations contain from 140 - 400 IU Vitamin D and 1,000 - 2,500 IU Vitamin A. Others also contain between 10 - 18 mg elemental iron per tablet.
- Dogs occasionally ingest large (50 - 200 tablets) quantities of the multivitamins.
- Vitamin A and D ointments contain Vitamin A at approximately 1,350 IU/g and Vitamin D at approximately 270 IU/g of ointment.

**Toxicity**

- The NCR daily recommended requirement of Vitamin D for growing dogs is 22 IU/kg.
- Historically, Vitamin D poisoning had been associated with chronic oversupplementation. Chronically administered (1 - 3 weeks) Vitamin D may cause toxicosis at 2,000 - 4,000 IU/kg.
- Acute Vitamin D toxicosis in the dog has been reported following the ingestion of 64,000 - 460,000 IU/kg.
- **Note** (Regarding multivitamin and iron preparations):
  - Vitamin A toxicosis in humans occurs if Vitamin A is ingested in excess of 25,000 IU/kg.
  - Iron toxicosis may occur if 40 - 60 mg of iron/kg are ingested.

**Treatment for Vitamin Supplement Ingestions**

- Often none required.
- Emetics, activated charcoal.
- See Treatment section for Animals Exposed to Cholecalciferol Rodenticides.

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### Additional Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Nephrotoxic Organic Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillage liquid from ethanol production</td>
<td>Cattle</td>
<td>(Syndrome not yet confirmed)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td></td>
<td>(See Hepatotoxic Chemicals and Drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenolics</td>
<td></td>
<td>(See Hepatotoxic Chemicals and Drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carp gallbladders (ingestion, from any of several species of carp; uncooked)</td>
<td>-</td>
<td>-</td>
<td>Days to weeks; potentially lethal</td>
<td></td>
</tr>
<tr>
<td>Diquat (Herbicide)</td>
<td>Most species</td>
<td>Few days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
References

**Vitamin K<sub>3</sub> (Menadione)**

**Blister Beetle - Cantharidin Toxicosis**

**Sulfonamides**

**Amphotericin B**

**Other Nephrotoxic Antibacterial Agents**

**Carbamate Fungicides**

**Analgesic Nephropathy**

Cholecalciferol-Based Rodenticides and Other Vitamin D-Containing Products

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