‘What horses should NOT eat – common and uncommon poisonings in horses’

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**IONOPHORES**

**Source**

Feed additives – mono(di)valent polyether antibiotics. Given orally, they alter microflora populations and this leads to: increased feed efficiency and rate of weight gain (increased production of volatile fatty acid propionic acid by rumen bacteria and enhances nitrogen retention by improving nitrogen digestibility); decreased incidence of bloat and lactic acidosis (kills off lactobacilli); decreased incidence of bovine pulmonary emphysema (reducing the conversion of L-tryptophan to 3-methylindole by the ruminal bacteria); coccidiostat.

**Toxicity**

Varies between species and the specific ionophore. Toxicosis may result from a single dose (target and nontarget animals) or can occur after daily lower level exposures (not long though), especially in species where it is legally used as a feed additive.

<table>
<thead>
<tr>
<th>Monensin</th>
<th>LD$_{50}$ Horse 1-2 mg/kg</th>
<th>Approximate Single Toxic/Lethal Dose 1-2 mg/kg</th>
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</thead>
<tbody>
<tr>
<td>Lasalocid</td>
<td>LD$_{50}$ Horse 21.5 mg/kg</td>
<td>Single Toxic Dose 15 mg/kg</td>
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<tr>
<td>Laidlomycin</td>
<td>Equine 14 day feeding trial: 11 ppm diet → no effect, no aversion 55 ppm diet → mild aversion and mild signs 165 ppm diet → toxic within 5 days 440 ppm diet → toxic within 1-2 days</td>
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All species susceptible – toxicity and sensitivity varies between products.

**Typical scenario – one time exposure** or daily lower level exposure / usually a history of feed change within last few days.

Conditions conducive to poisoning - improper mixing; math error; partitioning (rise to top), exposure of therapeutic doses for food animals to susceptible species (dogs, horses), feeding poultry litter.

Concurrent use of some drugs (e.g. oleandomycin, chloramphenicol, sulfonamides, tiamulin, dihydroquinolones) will decrease therapeutic effect 10 fold and increase toxicity 8 fold. This is due to a decrease in metabolism of the ionophores – macrolide antibiotics decrease rate of ionophore clearance.

Affects excitable membranes more than others - e.g., cardiac and skeletal muscle.

Will sequester short term in adipose tissue; no long-term sequestration.
Mechanism of Action

- Absorption from gastrointestinal tract is low - most passes through feces.
- Rapidly metabolized by liver in first-pass effect - metabolites excreted into bile. Very small amounts enter systemic circulation.
- Forms lipid soluble complexes with mono and divalent cations facilitating transport of them across the membrane along a diffusion gradient. Transports primarily sodium into cells (proton exchange results in acidosis and potassium loss). High intracellular sodium leads to secondary calcium influx, mitochondrial swelling, inhibition of oxidative phosphorylation, cell necrosis and death. All results in early positive ionotropy (myocardial, skeletal contractility), but later negative ionotropy (skeletal and cardiac muscle dysfunction). Smooth muscle spared; striated muscle pathology predominates (? differences in cell membrane matrix - fatty acids?).

Clinical Signs

- Latency period (and signs) varies depending on species, age, diet, ionophore, and most importantly dose: 1-2 hours (death with no signs) up to 2-3 weeks (death may occur several months later due to cardiac or respiratory insufficiency): average is 12-72 hours. Where skeletal muscle pathology predominates - death due to respiratory depression occurs within first 48 hours.
- The most common clinical manifestations are partial to complete feed aversion - animals will eat other foods, diarrhea, weakness, ataxia, dyspnea, depression, tachycardia. Signs: cardiac vs skeletal – may affect one or other or both, depending on species!
  - Horse – cardiac predominates, along with GI
    - Single lethal ingestion – Feed aversion, colic, ataxia, recumbency, tachycardia, arrhythmia, abnormal pulmonic sounds - death within 48 hours.
    - Non-acute single lethal dose (sub-acute myocardial damage) - Cardiac tamponade, pleural edema, ascites, respiratory dyspnea, arterial hypotension, venous hypertension - death within 10 days.
  - Sudden death - Acute cardiac failure (cardiac arrhythmia?).

Clinical Pathology - Fairly nonspecific.

- Look for: ↑ bilirubin.
- May see: ↑ creatine kinase, ↑ lactate dehydrogenase, ↑ aspartate transaminase, ↑ glucose, stress leukogram.
- May see: EKG alterations (not in poultry): S-T segment depression, T wave depression, atrial fibrillation. Not helpful in diagnosing because most animals dying with myocardial necrosis have normal EKG 24 hours prior to death.
- May see: myoglobinuria, hematuria, azotemia, hypokalemia.
- Troponin levels – not specific to ionophores.

Pathologic Lesions: Some animals may die acutely showing no significant lesions. Lesions are most pronounced in animals dying several days after ingestion of a toxic dose.

Gross: Horse, Cattle, Poultry (cardiac pathology predominates): Pleural, pericardial and peritoneal effusions, pulmonary edema, pericardial and epicardial hemorrhages, pale myocardium, ventral edema, enlarged liver

Microscopic: Animals dying peracutely may show no significant lesions. Lesions may have focal distribution so intense sampling is a must. May see:
  - Heart: pale myofibers, loss of fiber striation, multifocal vacuolar degeneration and necrosis; variable inflammatory component.
  - Skeletal muscle: severe degeneration/necrosis of type I muscle fibers.
  - Kidney: acute tubular necrosis.
Liver: centrilobular necrosis, mild fibrosis, congestion.
Sensory and motor n.: varying degrees of axonal degeneration and destruction of the myelin sheath - highly time dependent.
Pancreas: zymogen granule depletion

Diagnosis
- History of change of feed – within 3 days of problems.
- Clinical signs in appropriate species.
- Cardiac / Skeletal lesions.
- Feed analysis - will confirm, especially if present in greater than recommended use levels.
- Feces, serum, bile, liver, and GI contents - analyze for ionophores.

In general, stomach contents and tissues are not useful samples for ionophore analysis in target species. Blood levels are low or undetectable and accumulation does not occur in tissues to a significant extent. Analysis of tissues may be helpful to indicate exposure in nontarget species. In target animals, no known ‘normal’ and ‘toxic’ levels.

Treatment
Acute scenario - rare. Decontaminate if appropriate - emesis, AC + cathartic, mineral oil. ‘Supportive’ care. Decrease ionophore levels to normal in target animals – don’t want to change rumen microflora any more than already have. Remove in nontarget animal’s diet/environment.

Primarily supportive - selenium/vitamin E may afford some protection – prior to onset of exposure or signs. IV lipid infusion??
Withdrawal period? (overdose is “off label use” so label withdrawal does not apply)….30 days?
Long-term problems: cardiac insufficiency → production loss; skeletal fibrosis → performance loss.

SLOBBERING DISEASE

Source
- Fungus Rhizoctonia leguminicola infects red clover (Trifolium pratense) - “black patch”.
- Slaframine is the mycotoxin - cool, wet weather - indolizidine alkaloid.
- Stable and persists.
- May affect other clovers; alfalfa; other legumes.

Toxicity // Mechanism of Action
- Mimics the action of acetylcholine, with parasympathomimetic effects.
- Cattle, horses, sheep, goats commonly affected.
- Levels > 10 ppm associated with disease.

Clinical Signs
- Within 1-3 hours after consumption // Subside pretty quickly (12-48 hrs) if no re-exposure occurs.
  - profuse salivation
  - mild lacrimation
  - bloat
  - stiffness
- frequent urination
- drop in milk production
- diarrhea

Diagnosis

✓ Appropriate feed - moldy clover or other legumes
✓ Clinical signs - slobbering
✓ Lack of specific oral lesions
✓ Confirmation:
  mold ID (NOT)
  slaframine analysis – can do on feed

Treatment

Remove feed – some don’t worry – just keep slobbering
Atropine – probably NO NEED
Recover quickly

Perennial Ryegrass Staggers

Source

. Toxic endophyte, Acremonium lolii (Neotyphodium lolii), found on lower leaf sheath of perennial rye grass (Lolium perenne). Other grasses may be involved. Also found in seeds.
. Occurs late summer and fall when grass stubble is 3-5 cm tall. Hay problem as well.
. Symbiotic relationship between endophyte and plant – fungus growing within a plant [cannot see].

Toxicity / Mechanism of Action

. Reported in cattle, sheep, horses, deer, elk.
. Under certain conditions, fungus produces a group of toxins called: lolitrems (indole-based alkaloids).
. May affect Purkinje cells.
. Some strains producing high levels of lolitrem may also produce ergovaline.
. Morbidity is very high / Mortality very low if animals moved to safe pastures.

Clinical Signs

. Onset within 7-10 days (variable) of continuous exposure to infected grasses - depends on length of grass or if seed heads are present.
  - Fine muscle tremors of the head and neck.
  - Uncoordinated, jerky gait which may affect forelimbs and progress to hind limbs.
  - Signs are exacerbated when stressed or forced to move or heads covered (if allowed to rest, look normal in 5-10 minutes).
. Clinical signs will abate within a few days of removing to clean pasture. Severely affected animals may take 2-3 weeks to recover.

Clinical Pathology / Lesions: nonspecific.

Diagnosis // Control
History of grazing perennial ryegrass or ingesting PRG hay.
√ Clinical signs when aggravated / Recovery after moved into clean environment / High morbidity but low mortality

Analyses:

- Fungal identification - light microscopy – unique morphological features within epidermal sheaths
- Fungal culture - tedious
- Lolitrem analysis – quantifies (suggested sampling techniques)
- Bioassay // Feeding trial

√ Remove from contaminated feed (allow regrowth if in a pasture), supplement with good quality feed, replant pasture (replace with endophyte-free). ASSUME your PRG is infected until proven otherwise. Avoid overgrazing and use rotational system.

Acer spp.
maple - red maple in particular

Toxic Principle: Unknown (some type of oxidant; gallic acid has been implicated). Wilted or dried leaves are especially toxic; (lethal dose of leaves: 1.5-3.0 g/kg BW; 0.5 to 0.8% BW of dried green leaves; 1.5 to 3.0 g leaves/kg BW toxic). Reported most commonly in late summer and fall. Should consider all Acer spp. potentially toxic.

Mechanism of Action: Unidentified toxin (some type of oxidant damage) causes an acute hemolytic anemia, methemoglobinemia, and Heinz body formation.

Animals Affected: Almost all reports have been in horses; report in two alpacas.

Clinical Signs // Clinical Pathology: Appear in less than 48 hours. Include depression, anorexia, cyanosis, icterus, tachycardia, polyuria, brown discoloration to blood // Anemia, methemoglobinemia, hemoglobinuria, Heinz bodies.

Pathologic Lesions: Generalized icterus, splenomegaly, hepatomegaly / Centrilobular hepatic degeneration, hemoglobinuric (hypoxic?) nephrosis, erythropagocytosis by splenic, adrenal, and hepatic macrophages.

Cruciferae (Mustard Family)

Toxic Principles // Mechanism of Action: Vary with plant and plant part. The majority of these plants will be harmful to animals only under certain specific conditions which have not been well characterized.

1. Indole glucosinolates (derived from tryptophan) converted to isothiocyanates (volatile oils) upon mechanical breakdown of plant or seeds. Isothiocyanates are gastrointestinal irritants.
2. Other breakdown products of glucosinolates are S-vinylloxazolidine-2-thione (goitrin - comes from progoitrin via myrosinase) and thiocyanate ion. The former interferes with thyroid hormone synthesis and thiocyanate ion competes with iodine for uptake by the thyroid gland.
3. S-methyl cysteine sulfoxide undergoes breakdown to dimethyl disulfide - causes hemolytic anemia.
4. Many will accumulate nitrate under conditions of heavy nitrogen fertilization or stress.
5. *Pneumotoxic metabolite* (maybe similar to 3-methyl indole) responsible for acute pulmonary emphysema and edema.

6. High *thiaminase*-like activity or high S content associated with *poloencephalomalacia* and *copper deficiencies*.

7. Other less commonly encountered syndromes: *Rapeseed* in particular has been associated with *reversible blindness* and *hepatic necrosis* accompanied by *photosensitization*. May also see bile duct hyperplasia and megalocytosis of renal tubular epithelium. Have been reports of *bloat*, various *reproductive inefficiencies*, and *enterotoxemia* in various species grazing these plants. The glucosinolates and their metabolites are transferred into the milk.


Diseases of cattle that graze turnips: bloat, pulmonary emphysema, polioencephalomalacia, anemia // reproductive inefficiency, hypothyroidism, nitrate poisoning, copper and iodine deficiencies, enterotoxemia.

**Clinical Signs // Pathologic Lesions:** Depends on species affected, amount and type of plant ingested.

1. Abdominal pain, vomiting, diarrhea.
2. Enlarged thyroid glands or normal size thyroid glands that are hyperplastic; increased anestrus; affected young often born weak and die shortly after birth.
3. One to three weeks after ingestion, see jaundice, hemoglobinuria (may not see acute hemolysis with significant hemoglobinuria - more often see a low grade anemia which has a deleterious effect on health and productivity), anorexia, fever // Macrocytic hypochromic in cattle, microcytic normochromic in sheep, Heinz body formation // Swollen pale liver, jaundice, dark brown kidneys, splenomegaly // Hepatic and renal hemosiderosis, renal tubular degeneration.
4. See nitrate accumulators (class notes).
5. Acute onset of tachypnea, expiratory dyspnea // Lungs are bilaterally rubbery, wet and heavy; blood-tinged fluid fills alveolar and interstitial spaces // Prominent emphysematous distension of interlobular septa.
6. Twitching of ears and eyelids, champing of jaws, blindness, wandering aimlessly, progress to recumbency, nystagmus, convulsions // Cerebral edema, thinning and yellow-gray discoloration of the occipital and parietal cortices // Laminar cortical necrosis, accumulations of microglia filled with cytoplasmic lipid vacuoles.
7. High S content interferes with copper absorption.
8. **Dysmaturity syndrome in foals:** incomplete ossification, mandibular prognathism, tendon rupture.
9. Cholesterol levels often drop in animals grazing Brassica spp.

**Treatment:** Depends on severity of clinical signs, species affected, etc.

1. Symptomatic and supportive.
2. Supply iodine to diet. Affected animals have poor prognosis.
3. Symptomatic and supportive (e.g., blood transfusion, fluids, electrolytes, antibiotics).
4. See nitrate accumulators (class notes).
5. Symptomatic and supportive (furosemide - 0.4-1.0 mg/kg IV, IM every 12 hrs; flunixin meglumine - 2.2 mg/kg IV sid) - mortality rate is usually high.
6. Thiamine hydrochloride (10 mg/kg IV, then 10 mg/kg IM bid for 2-3 days - cattle), mannitol, dexamethasone.
7. Supplement with copper.
8. Supportive – supplement with selenium.

**Pyrrolizidine Alkaloid Containing Plants:** Senecio spp., Amsinckia intermedia, Cynoglossum officinale, Heliotropium curassavicum, Crotalaria spp., Echium spp.
**Toxic Principles**: Toxic pyrrolizidine alkaloids - many have been isolated and characterized. The pyrrolizidine alkaloids vary between species of plant, genera of plant, and the concentrations vary within each individual plant depending on age and maturity, part of plant, and environmental conditions. **Examples** are: *Senecio* spp. - senecionine, jacobine, jacobidene, riddelline, longilobine, seneciphylline, retrorsine, jaconine, jacoaine, olosenine, senkirkine, integermine, spartoiidine, usaramine; *Cynoglossum* - 7-angelylheliotridine, echinatine, heliosupine, acetylheliosupine; *Heliotropium* - heliotrine, lasiocarpine, curassavine, heliovicine, etc.; *Amsinckia* - intermedine, lycopsamine, echiumine, sincamidine, echimidine. Toxicity varies greatly depending on species and age of plant and species of animals affected. In general, toxicosis may result from grazing heavy stands, ingesting seeds in grain mixes, or eating contaminated hay for long periods of time - 30 days to several months. Usually requires between 1-5% of an animal's BW of plant material in the diet. In some instances, may be higher, up to 50% of BW. The pyrrolizidine alkaloids can cross the placenta and affect the developing fetus and are also excreted into the urine and milk. Some of these alkaloids have been shown to be carcinogenic, so there is quite a bit of human health concern.

**Animals Affected**: Cattle, horses, and swine most commonly affected. Sheep and goats are relatively resistant - either due to altered rumen degradation or differences in hepatic metabolism. Poultry also susceptible.

**Mechanism of Action**: All pyrrolizidine alkaloids are rapidly absorbed from the gastrointestinal tract and immediately undergo metabolism within the liver by the mixed function oxidase system to the actual ultimate toxic metabolites which are highly reactive pyrroles. The pyrroles alkylate macromolecules within the hepatocytes (which are readily available), primarily DNA, which thus impairs cell division. The cell continues to grow and both the nucleus and cytoplasm expand (hepatocytomegaly and karyomegaly), but is unable to divide. Ultimately a critical mass is reached and cell necrosis begins. The toxic effects are cumulative in nature.

**Clinical Signs**: Dependent on degree of liver damage. Signs are associated with hepatic insufficiency - these can include weakness, loss of condition, weight loss, icterus, crusting and scaling of skin due to secondary photosensitivity; and a variety of nervous signs associated with hepatic encephalopathy - derangement, mania, drowsiness, yawning, walking aimlessly, ataxia.

**Clinical Pathology** often reveals elevation in several liver enzymes, particularly glutamate dehydrogenase, gamma-glutamyltransferase, and alkaline phosphatase.

**Pathologic Lesions**: Grossly, liver may be enlarged or cirrhotic depending on whether it is acute or chronic. Histologically, hepatocytomegaly, bile duct proliferation and fibrosis (regenerative response to death of large numbers of hepatocytes) are the predominant features. Analysis of liver and blood for presence of pyrroles is available. Megalocytosis not specific for PA can see with aflatoxin, nitrosamine, and lantana.

**Treatment**: Symptomatic and supportive only. Usually is not successful once severe clinical signs have appeared.

♀ *Trifolium hybridum* (alsike clover), *Trifolium pratense* (red clover) ♀

**Toxic Principle // Mechanism of Action**: Unknown - ?mold-mycotoxin or plant toxin?. Disease associated with *Cymodothea trifolii* - fungus responsible for black blotch or sooty blotch. Another hypothesis: *Capnocytophaga* - endophytic bacteria. Various glycosides and volatile oils have been isolated. Two conditions occur: liver disease and trefoliosis (secondary photosensitivity). Contact dermatitis ("dew poisoning") of the feet and muzzle has also been reported. Try to keep < 20% of diet.

**Animals Affected**: So far, it has only been reported in horses.

**Clinical Signs**: Onset within 7-30 days - variable depending on percentage in diet. Two clinical manifestations - (1) *Acute or nervous form*: alternating depression and excitement, head pressing, purposeless walking, incoordination,
yawning, grinding teeth, and then rapid progression to paralysis, coma, and death; and (2) **Chronic or cachectic form**: anorexia, loss of condition, weakness, sluggishness, dry harsh hair coat.

**Clinical Pathology**: Most consistent changes are elevations in GGT and AP - less commonly affected are AST, ALT, and SDH. Bile acids, ammonia, and total bilirubin may be elevated - icterus is not a consistent change.

**Pathologic Lesions**: Liver can be normal, enlarged, or shrunken, jaundice // Perilobular-centrilobular-periportal fibrosis, bile duct proliferation - parenchyma is almost unaffected - varying degrees of inflammation and necrosis / may occasionally see lipidosis and megalocytosis.

**Treatment**: Symptomatic and supportive only.