Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well) (9-Aug-1999)

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1. Toxicants that Act as Cholinergic Blockers

Background

Acetylcholine is the neurotransmitter of cholinergic neurons in the autonomic and central nervous systems.

Anticholinergic-Synonyms

- Cholinergic blockers.
- Antimuscarinic.
- Antiparasymathtic.
- Cholinolytic.
- Parasympatholytic.
- Antispasmodic.
- Spasmolytic.

Cholinergic neurons:
- Include all sympathetic and parasympathetic preganglionic neurons and nerve supply to the adrenal medulla.
- Parasympathetic postganglionic neurons (autonomic effector sites).
- Sympathetic postganglionic neurons which innervate sweat glands.
- Sympathetic postganglionic neurons which innervate blood vessels in skeletal muscle and produce vasodilation when stimulated.
Types of postsynaptic Cholinergic Receptors

<table>
<thead>
<tr>
<th>Cholinceptive Site</th>
<th>Autonomic Effector Cell</th>
<th>Autonomic Ganglion Cell</th>
<th>Striated Muscle</th>
<th>Central Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinomimetic Agent</td>
<td>Muscarine</td>
<td>DMPP(Ng) McN-A-343 (M1)</td>
<td>PTMA</td>
<td>Muscarine, Oxotremorine, Carbachol</td>
</tr>
<tr>
<td>Cholinergic Blocking Agent</td>
<td>Atropine</td>
<td>d-TC</td>
<td>d-TC</td>
<td>Atropine, d-TC</td>
</tr>
</tbody>
</table>

Receptors

- There are three (3) categories of cholinergic receptors: muscarinic, nicotinic, and CNS.

1. Muscarinic receptors (M1, M2):
   - Smooth muscle.
   - Cardiac muscle.
   - Exocrine glands.
   - CNS.
   - Transmitting agents.
     - Acetylcholine in normal concentrations.
     - Muscarine.
   - Non-depolarizing blocking agents include:
     - Atropine and other belladonna alkaloids.

2. Nicotinic receptors (N):
   - Autonomic ganglia.
   - Skeletal muscle (Nm).
   - CNS.
   - Transmitting agents.
     - Acetylcholine in normal concentrations.
     - Nicotine in low concentrations.
   - Blocking agents.
     - Nicotine in high concentrations produces a depolarizing blockade of ganglia and skeletal muscle.
     - Acetylcholine also causes a depolarizing blockade at very high concentrations as occurs with serious toxicosis due to cholinesterase inhibitors, i.e., organophosphorus or carbamate insecticides.
     - Curare - Causes a non-depolarizing blockade at skeletal muscle (neuromuscular receptors). Active agent = d-tubocurarine = d-TC.
     - Nicotinic sites are not highly sensitive to atropine.

3. Central nervous system receptors (M1, M2, N, possibly others).
Nondepolarizing Blockers at Muscarinic (Cholinergic) Receptors

Introduction

- Parasympatholytic agents prevent acetylcholine (Ach) from producing its effects at muscarinic receptors in the brain and at postganglionic receptors.
- Inhibit effects of Ach on Ach responsive nerves, smooth muscle cells, and glands, i.e., innervated by sympathetic postganglionic cholinergic fibers (muscarinic receptors).

Sources

- Various drugs in some antispasmodics, antihistamines, antipsychotics, antidepressants, and some over-the-counter sleep preparations act as non-depolarizing blockers of muscarinic receptors.
- Scopalamine ophthalmic solution 0.25% and atropine ophthalmic solution (up to 4%).

Atropine (DL-Hyoscyamine)

- A natural tropane alkaloid extracted from the belladonna plant (*Atropa belladonna*), a nightshade shrub. Principle alkaloid in jimson weed (*Datura stramonium*).
- Tincture and extract of belladonna may still be encountered in homes.

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<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><strong>Atropine</strong> (D, L hyoscyamine)</td>
<td>Cattle, dogs, cats, and esp. horses</td>
<td>Minutes</td>
<td>Hours to a day in small animals, horses (up to 3 days); up to several days in cattle; potentially lethal, esp. in horses</td>
</tr>
<tr>
<td><strong>Scopolamine</strong> (L-hyoscine)</td>
<td>Effects similar to atropine; toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benztropine</strong> (Cogentine ®)</td>
<td>Effects similar to atropine; toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aminopentamidine</strong> (Centrine ®)</td>
<td>Effects similar to atropine; toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atropine methyl nitrate</strong></td>
<td>Toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scopolamine methyl bromide</strong></td>
<td>Toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Homatropine methyl bromide</strong></td>
<td>Toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Propantheline</strong> (Pro-Banthine ®)</td>
<td>Toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Glycopyrrolate</strong> (Robinul-V ®)</td>
<td>Toxicosis unlikely when used at recommended doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Atropine is a tertiary amine - not charged (penetrates blood-brain barrier).
Atropine methyl nitrate is charged (little penetration of BBB).
Belladonna alkaloids are rapidly absorbed from mucous membranes.

**Scopolamine (L-Hyoscine) (Epoxidized Hyoscyamine)**

- Occurs in the *Henbane* plant (*Hyoscyamus niger*) and in jimson weed (also called Jamestownweed) (*Datura stramonium*) and a derivative, stramonium powder.
- The L-isomers are more potent both in peripheral and central nervous systems.

**Classes of Drugs**

- Tertiary amines-no charge-penetrate CNS, e.g. atropine, scopolamine.
  - Benztropine (Cogentine) used in treatment of Parkinsonism.
  - Ophthalmics.
- Quaternary analogs-charged, therefore do not tend to enter CNS.
  - Atropine methyl nitrate.
  - Scopolamine methylbromide.
  - Homatropine methylbromide.
  - Propantheline (Pro-Banthine).
- Certain antihistamines, antidepressants, and antipsychotics also have cholinergic blocking properties.

**Mechanism**

Atropine does not affect acetylcholine release. However, atropine and all of the parasympatholytic drugs act as competitive antagonists at acetylcholine receptors where acetylcholine exerts a parasympathomimetic or muscarinic effect. Also, the effects of acetylcholine receptors beyond parasympathetic postganglionic endings are blocked. However, following atropine administration, acetylcholine still exerts its sympathomimetic and nicotinic effects, including acting at voluntary muscle receptors.

**Absorption, Distribution, Metabolism and Excretion (ADME)**

- Variable oral absorption, normally prolonged in toxic doses due to decreased GI motility.
- Metabolized in liver to tropic acid, tropine and esters of tropic acid and has glucuronide conjugates formed.
- Elimination half-life (man) 2 - 3 hours, longer in children.

**Toxicity**

Low doses of atropine (0.044 mg/kg) decreased GI motility for 8 - 12 hours in horses.

**Signs**

- Produces both peripheral and CNS symptomatology.
- Blocks vagus-rapid heart rate at high enough doses (low doses may stimulate vagal medullary centers causing bradycardia). Ventricular arrhythmias and EKG changes (widened QRS, prolonged QT interval) may occur.
- Urinary retention, constipation.
- Dry mouth.
- Decreased gastrointestinal motility, occasionally vomiting. **Colic in horses.**
- Some mild CNS depression can occur, CNS stimulation may precede depression. Behavioral changes may occur, e.g., "disorientation", hallucinogenic in man.
- Mydriasis, pupils may be unreactive to light.
- Loss of accommodation (cycloplegia)-cannot see well up close, distant vision remains sharp.
- Hyperthermia, hypertension, ataxia, dysphagia.
- Very high doses, coma and skeletal muscle paralysis may occur.
- Drop of urine obtained from an atropine-poisoned animal may cause mydriasis if placed into another animal's eye. Occasionally used as a diagnostic aid.

**Treatment of Poisoning**
Activated charcoal, saline cathartic-for recent oral exposure.
Do not use phenothiazine tranquilizers.
For severely poisoned:
- **Very** slow IV-physostigmine to the point at which delirium and coma are abolished or SQ (see below).
Monitor EKG-in general sinus tachyarrhythmias, do not need to be treated (slowed) unless signs of cardiac insufficiency develop. Tachyarrhythmias unresponsive to physostigmine may respond to propranolol administered at 0.2 mg/kg (dog dose) IV, slowly.

**Physostigmine**
- Indications in treatment of atropine or other cholinergic blocker overdose:
  - Diagnostic tool.
    - If administered slowly IV over 5 minutes and if get recovery, the diagnosis is confirmed. Begin with 0.5 mg total dose (based on human pediatric doses), may need to be repeated.
    - Animal could fail to recover if:
      - Previously anoxic: may already have brain damage.
      - If ingested a combination medication.
    - Life threatening toxicoses-as a treatment, i.e., for atropine poisoned animals which display a notable amount of:
      - Convulsions.
      - Hypertension.
      - Arrhythmias: use with caution, physostigmine can cause asystole.
    - Do not give repeatedly just to keep awake. The lowest total effective dose should be administered, no more often than every hour.
  - Dosage
    - A pediatric therapeutic trial dose is 0.02 mg/kg slow (over 5 minutes) IV.
    - Recommended at 0.055 mg/kg (1 mg/18 kg) for dogs slow (over 5 minutes) IV.
    - Recommended for horses at 0.1 - 0.6 mg/kg IM or slow (over 5 minutes) IV.

**Note**
- **Physostigmine**: a naturally occurring carbamate alkaloid = eserine = obtained from Calabar bean = ordeal bean
- Physostigmine is hydrolyzed by cholinesterase but much slower than acetylcholine.
  - Physostigmine therefore competitively inhibits cholinesterase and less acetylcholine is degraded.
  - Results in elevated concentrations of acetylcholine which compete with atropine for the cholinergic receptor (nicotinic, muscarinic, or gland).
  - Physostigmine is **not charged** so that it penetrates the CNS.
- Charged analogs - such as neostigmine (Prostigmine); pyridostigmine (Mestinon), benzpyrinium (Stigmonene), and decamarium (Humorsol) are quaternary ammonium analogs which do not efficiently penetrate the BBB. Since the primary lethal effects of atropine toxicosis are central, these are not used in treatment of atropine toxicosis.
Atropa belladonna - Belladonna Plant

Synonyms - Deadly nightshade (a Solanaceae member), nightshade, sleeping nightshade

Images

- Belladonna, Atropa belladonna. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Belladonna, Atropa belladonna - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Description

*Atropa belladonna* is a coarse herb with a thick root, and with highly branched stems which grow from 0.6 - 1.6 m tall. The leaves are large (approximately 15 cm [6 inches] long), ovate, and alternately inserted but develop so rapidly that they may appear to be inserted in pairs at the same point with one member of each pair larger than the other. Flowers are solitary, almost 2.5 cm long, 5 parted, with a 5-pointed calyx, a tubular corolla, and dull purple. Single berries (1 - 1.3 cm in diameter) are purple to black when ripe. Reddish sap.

Habitat

Native to Europe, a garden plant in the USA - Occasionally encountered, rarely escapes from gardens but forms no extensive growths.

Toxicity

- Atropine, which is present throughout the plant, increasing to maximum at maturity.
- Ingestion of as few as 3 berries was fatal to a child.

Signs

Poisoning is rare. Trembling, excitement, followed by prostration in about 10 hours. Tachycardia, weak pulse, extreme mydriasis, difficulty in short range vision (accommodation), dyspnea, gastric and/or intestinal atony, coma, hyperthermia (in humans and perhaps in animals that sweat), death.

Diagnosis

Evidence of consumption, presence of atropine effects, placing a drop of urine into a cat's eye causes mydriasis.

Treatment

As for atropine ingestion (see Introduction to Anticholinergic Agents section).
Deadly Nightshade - *Atropa belladonna*
Henbane (Hyoscyamus niger)

Synonyms

- Black henbane, henbane, stinking nightshade, poison tobacco, fetid nightshade, and insane root.
- Another member of the Solanaceae.

Images

- Henbane, Hyoscyamus niger - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Description

An annual or biennial, coarse, hairy, erect herb, 1 - 4 feet tall with coarsely toothed, oblong leaves 3 - 8 inches in length. Flowers are single on short pedicels or in the leaf angles becoming crowded near the tips. Flowers are 5 lobed with greenish-yellow or yellowish-white with a purple throat and veins. Fruits are enclosed in a 5 lobed capsule. Spindle-shaped roots.

Habitat

- In the USA, primarily found in the northeastern states.
- Scattered in southern Canada, northern USA, locally common in some areas of the northern Rocky Mountain states.
- Usually in dry soils, in roadsides, other "waste areas".

Toxicity

- Atropine and scopolamine.
- The seed is poisonous.

Susceptible Species

- Has poisoned livestock, children.
- Fowl were poisoned from eating seed.

Signs

- Similar to other anticholinergic poisoning.
- Poisoning is rare, perhaps because the plant is distasteful.

Treatment

- As for atropine ingestion (see Introduction to Anticholinergic Agents section).

<table>
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<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
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</thead>
<tbody>
<tr>
<td>Poultry, cattle, sheep</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
</tr>
</tbody>
</table>
Hyosycamus niger
**Datura stramonium - Jimson Weed**

### Synonyms
- Jamestown weed, thornapple, devil's trumpet, mad apple, and stink weed.
- Solanaceae member.

### Images
- *Datura* spp. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Jimson weed, *Datura stramonium* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

### Description
- Plant is a stout, coarse, annual herb which is 0.6 - 1.6 m tall with spreading branches and simple alternate leaves (15 - 20 cm [6 - 8"] long) which are coarsely and irregularly toothed with a rank odor.
- Flowers are large, white or purple and tubular; 5 - 10 cm (2 - 4") long.
- Fruit is a spiny capsule 2.5 - 5 cm (1 - 2") in diameter which can be split into four parts. Sheds small brown to black seeds; seeds contaminate corn, etc.

### Habitat
- Fertile soils where other plants are scarce - e.g. barnyards, fertile cultivated fields, hog lots.
- Midwest as far north as southern Minnesota, Wisconsin, Michigan.

### Toxic Principle
- Tropane alkaloids:
  - Hyoscyamine = an isomer of atropine.
  - Scopolamine = L-hyoscine = epoxidized hyoscyamine.

### Toxicity
- Poisoning is infrequent; regarded as unpalatable.
- Poisoning occurs primarily when hungry animals are turned into an area where better forage is absent.
- Poisoning may also result when a large amount is present in hay.
- Palatability may increase when sprayed with 2,4-D or similar herbicides.
- Possible poisoning as a result of seeds in grains and feeds (seeds contain 0.05% alkaloid by weight).
- Entire plant is toxic, seeds most often implicated.
- Pigs appear to be very sensitive to seeds, 2.2 - 2.7 mg/kg/day reported to cause toxic signs.
- Toxic signs seen in cattle given seeds at 0.06 - 0.09% bw/day.

### Signs
- Hypothermia in animals, hyperthermia in man. Death from respiratory paralysis.
Depression, anorexia, weight loss, tachypnea, tachycardia, mydriasis, polyuria, polydipsia, diarrhea.

In cattle see excitability, tremors, rumen atony, nervousness, bloat, tenesmus, and anorexia. Death occasionally reported.

In goats, *Datura stramonium* ingestion was accompanied by tachypnea, tremors, drowsiness, recumbency, and altered locomotion.

In sheep, *Datura stramonium* ingestion was associated with ataxia, inability to stand, tachypnea, reduced drinking and mild tremors.

**Treatment**

Similar to atropine ingestion (see Introduction to Anticholinergic Agents section).

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**Jimsonweed, *Datura stramonium* - L.** 1, upper portion of plant; 2, flower; 3, seed pod; 4, seed. **Annual**, reproducing by seed. **Roots** thick, shallow, extensively branched. **Stems** smooth, thick, erect, branching widely in upper part, 2 to 4 feet (0.6 to 1.2 m) tall. **Leaves** alternate, large, course, smooth, ovate, with irregularly toothed edges and a distinctive rank odor. **Flowers** large, funnel-shaped, white to pinkish, 2 to 5 inches (5 to 12.5 cm) long, borne singly on short stalks in the axils of the branches. **Seed pod** about 1 inch (2.5 cm) in diameter, egg-shaped, covered with short, sharp spines. **Seed** dark brown to black, kidney-shaped, flattened, surface irregular and pitted. **Found** in cultivated crops on rich land and especially in old feedlots. This plant contains poisonous materials.
**Anticholinergic Mushrooms**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostly small animals</td>
<td>Minutes to hours</td>
<td>Hours, rarely lethal</td>
</tr>
</tbody>
</table>

**Species**

*Amanita citrina, Amanita cokeri (solitaria), Amanita crenulata, Amanita muscaria, Amanita pantherina*, intergrade species of *Amanita pantherina, Amanita cothurnata, and Amanita gemmata*. Possibly *Panaeolus campanuiatus* and *Panaeolus* species.

**Images**

- *Amanita muscaria*. 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 .
- Google Image Search: *Amanita citrina, Amanita cokeri (solitaria), Amanita crenulata, Amanita muscaria, Amanita pantherina, Amanita cothurnata, Amanita gemmata*. - To view this image in full size go to the IVIS website at www.ivis.org .

**Description**

- *Amanita* sp. - large and colorful.
  - Ring around stem - "ring of death".
  - Cup on bottom of stem - "cup of death".

**Toxic Principle**

- Thermostable toxins--not removed by boiling. Not destroyed by drying.
- Contains isoxazoles (ibotenic acid, muscazone, and muscinol) cause most clinical signs. Pantherin, stizolobic acid, stizolobinic acid (L-dopa oxidation products) or tricholomic acid are also present. All of these have largely anticholinergic effects in the peripheral nervous system.
- Despite previous reports, there is no evidence that these mushrooms contain atropine (pilzatropine), hyoscyamine or stramonium.
- The isoxazole compounds apparently inhibit the effects of GABA which contributes to CNS dysfunction. The anticholinergic effects may sometimes be less appreciable.
- Occasionally small amounts of muscarine occur causing cholinerge effects, but usually these are clinically insignificant. Nevertheless, in some localities and some years the cholinerge symptoms predominate.

**Toxicity**

Fatality rate probably less than 1%, but reports are still inadequate. With appropriate treatment, an adult male human survived eating 20 large *Amanita muscaria*.

**Signs**

- Poisonings in small animals are rarely diagnosed.
- The anti-cholinergic syndrome includes both central and peripheral signs.
- The cholinerge effects of muscarine (when they occur) are mostly peripheral.
- Humans - onset within 30 - 60 minutes. Usually a feeling of drowsiness is quickly followed by a state of confusion resembling alcoholic intoxication. Dizziness, ataxia and euphoria may progress into hyperkinetic activity, muscle cramps and spasms, and even delirium. Visual disturbances and even hallucinations may occur, vomiting usually does not take place. Drowsiness to deep sleep or even coma terminate the episode which usually lasts for about four hours.
Diagnosis

Muscimol has been detected in the urine and, if analysis is available, may be used for confirmation of this type of ingestion.

Treatment

- Unless contraindications exist, emesis should be initiated. If contraindications are present, endotrachael intubation should precede gastric lavage. Lavage should be done with a large gastric tube. Activated charcoal and a saline cathartic should be administered after emesis (if not contraindicated) or lavage. Rapid action to prevent absorption is particularly important with this group of mushrooms since the latent period is so short. Spontaneous vomiting rarely occurs.
- Enhancement of excretion via forced diuresis is suggested with oral and IV fluids, and osmotic diuretics or furosemide.
- Treatment with physostigmine (as for atropine ingestion in Introduction to Anticholinergic Agents section) should be considered only if the anticholinergic effects (tachycardia, dilated pupil, hallucinations, decreased bowel sounds, dry mouth, etc.) are severe.
- Treat in response to, not in anticipation of clinical signs; they are variable.
- Atropine: only if cholinergic signs, e.g., severe bradycardia, is present.

*Amanita muscaria* - Wide red to yellow cap, white gills, and whitish stalk with wavy "skirt" and bulbous base are characteristic of this mushroom.
Introduction to Solanaceae, Solanine, Solanidine, Solanocapsine, as well as Atropine and Atropine-Like Toxins in the Solanaceae

Solanine

Solanine is a glycoalkaloid (sugar attached to an alkaloid). Because of the structure of the alkaloid portion of the molecule, solanine also is referred to as a steroidal alkaloid. The aglycone (sometimes called an alkamine aglycone) is called solanidine. The word aglycone simply means the compound remaining after the sugar moiety has been removed.

Overall Structure = Solanine

Sources

Solanaceae family.

Toxicity

- Glycoside (solanine) more toxic than aglycone (solanidine).
- Rapid fecal and urinary excretion.
- Toxic dose of solanine given orally to sheep was 225 mg/kg.
- See individual plants in pages that follow.

Absorption, Distribution, Metabolism and Excretion (ADME)

Solanine is poorly absorbed from GI tract.

Mechanisms of Action and Clinical Signs

- Principle effects of solanine alkaloid poisoning are gastrointestinal tract irritation and CNS impairment.
- Reportedly inhibits cholinesterase activity.
- Reportedly has weak cardiotonic activity.
- Depression, recumbency occurs in horses, cattle, swine.
- Exanthematous form-ulcerative stomatitis, conjunctivitis, diarrhea, and eczema of legs in cattle and pigs.

Signs

- The signs of poisoning due to solanine and atropine are somewhat parallel in that both may produce pupillary dilation, ataxia, muscular weakness, restless or thrashing movements, and body temperature elevation (the latter may occur with atropine toxicosis in animal species that sweat; not documented in animals; but occurs in atropine-poisoned humans).
- They differ in that solanine often produces gastroenteritis, depression, salivation, sweating in capable species and dyspnea. In man, headache is common, and stupefaction and loss of sensation have been reported.
Lesions

- Gastroenteritis.
- Congestion of cerebral membranes and kidneys.

Atropine, Structurally and Toxicologically Related Compounds and Solanocapsine

Some members of the Solanaceae have primarily solanine-type alkaloids (solanine, solanidine, etc.); others have atropine or atropine-like compounds; and still others may have both solanine-type as well as atropine-like constituents which complicate therapeutic considerations. Jerusalem cherry (Solanum pseudocapsicum), black nightshade (S. nigrum and other species), jessamine (Cestrum spp.) ground cherry (Physalis spp.), and tomato leaves and unripe fruit (Lysopersicon) often contain both solanaceous and atropine-like alkaloids and clinical signs from either may predominate. Potato (S. tuberosum) may also contain both types of alkaloid; however, the atropine-like constituents tend to predominate. In addition to the alkaloids mentioned above, Jerusalem cherry (S. pseudocapsicum) also contains solanocapsine, which produces marked bradycardia. These considerations are alluded to in the following sections.

*Physalis* spp. - Ground Cherry (Members of the Solanaceae)

*Physalis heterophylla* - Ground cherry, husk-tomato.

*P. subglabrata* - Ground cherry, husk-tomato.

Several other *Physalis* plants. Other trivial names for various *Physalis* spp. include Chinese or Japanese lantern plant, gooseberry tomato, strawberry tomato, winter cherry, and yellow henbane.

<table>
<thead>
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<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
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</table>

Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)

Images

- Clammy Ground Cherry (*Physalis heterophylla*) - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at www.ivis.org.
- Virginia Ground Cherry (*Physalis virginiana*) - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at www.ivis.org.
- Ground Cherry, *Physalis heterophylla* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- Ground Cherry, *Physalis subglabrata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Description

- There are a large number of *Physalis* spp. cultivated in the United States for their attractive Chinese lantern-like fruits.
  - *P. heterophylla*.
    - Erect, perennial herb, with branched or widely spreading, ridged stems. Leaves are alternate, broadly ovate, hairy. Flowers are solitary and in leaf axils. Flower is wheel-shaped to short-funnel shaped, 1.5 - 2.5 cm across, and with 5 parts. Yellowish in color.
**Geographical Location and Habitat**

- *P. heterophylla* - Eastern North America, westward to Texas.
- *P. subglabrata* - Eastern North America, southwestward to Arkansas and Colorado.
- Both plants grow in meadows, pastures and old fields.

**Toxic Principle**

The glycoalkaloid solanine + atropine-like alkaloids.

**Toxicity**

- Generally avoided unless forage is scarce.
- Large quantities of the tops and unripe berries may cause toxicosis in animals.
- Unripe fruit is most toxic.
- The berries of some species are edible when raw or cooked.

**Signs**

- Gastrointestinal upset, dyspnea, trembling, hyperthermia, weakness, and paralysis.
- Fatal poisonings have occurred in children.

**Lesions**

Gastrointestinal hyperemia, etc.

**Treatment**

- See *Solanum* and/or Introduction to Anticholinergic Agents section depending upon predominant signs.
- Fluid therapy and general supportive care as for gastroenteritis may be required.
Wright Groundcherry (*Physalis wrightii*) - The wavy-margined leaves, colorful flowers with flared openings, inflated seed pod (lower far left), and seed (enlarged, lower near left) characterize this southwestern forb.
Physalis subglabrata
Matrimony Vine

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
<td></td>
</tr>
</tbody>
</table>

Family - Solanaceae

Species

- Box thorn, false jessamine.
- *Lycium halimifolium*
- *L. carolinianum.*

Images

- Matrimony Vine, *Lycium halimifolium* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org -
- Matrimony Vine, *Lycium carolinianum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org -

Description

A woody, upright shrub or vine with curving pendant branches, up to 10 feet tall. The numerous branches occasionally bear long woody thorns. Flowers are solitary or few. Has 5 pointed green, bell-shaped calyces and a 5-lobed violet flower with 5 stamens. Fruit is a small orange or red berry about 2 cm in length.

Habitat

- *L. halimifolium*: was used as an ornamental shrub, some may be present in older plantings; now escaped and naturalized locally in northern USA and southern Canada.
- *L. carolinianum*: native to southeastern United States from Texas to Florida, north to South Carolina.

Toxic Principle

- Solanaceous alkaloids; probably like the glycoalkaloid solanine.
- Leaves are poisonous.

Toxicosis

Rare.

Signs

- Excitement, convulsions, death.
- Severe gastroenteritis noted at necropsy.

Treatment

See *Solanum* section.
Matrimony vine
(Lycium halimifolium)
**Cestrum spp.** - Jessamines

*Cestrum nocturnum* - Night blooming jessamine

*Cestrum diurnum* - Day blooming jessamine

Synonyms for both plants include Chinese inkberry.

<table>
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<th>Major Species</th>
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</thead>
<tbody>
<tr>
<td>Pet animals</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
</tr>
</tbody>
</table>

**Family** - Solanaceae

**Images**

- Day-blooming jessamine, *Cestrum diurnum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Night-blooming jessamine, *Cestrum nocturnum* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Description**

- Large, handsome shrubs with alternate simple entire, most lanceolate or elyptical leaves and axillary clusters of fragrant showy, trumpet shaped, 1 inch long, 5 parted flowers.
- In *C. diurnum*:
  - The flowers are white and sweet scented by day.
  - Ovate leaves 5 - 10 cm long.
  - Mature fruit is a globose, black berry.
- In *C. nocturnum*:
  - They are greenish and sweet scented by night.
  - Mature fruit is white.
  - Have longer (10 - 20 cm long) leaves.

**Habitat**

Frequently used ornamentals in southern states. *C. diurnum* may also be found wild in the Florida Keys and south Texas.

**Toxic Principle and Toxicity**

- In the unripe berry, solanine (the gastrointestinal irritant/cholinesterase-inhibiting glycoalkaloid: see Solanum) predominates
- In the ripe berry and the foliage, tropane (atropine-like) alkaloids are most prevalent.
- Saponins or traces of nicotine possible.
- *C. diurnum* may contain toxic concentrations of 1,25-dihydroxyvitamin D-glucoside (see section entitled Vitamin D-containing Plants).

**Susceptible Species**

Humans, pets.

**Signs**

Signs can be referable to any of the three toxins involved and will vary with species of the plant involved and its age.
Treatment

See *Solamum* and/or Introduction to Anticholinergic Agents section depending upon predominant signs. Also, see section on Vitamin D-containing plants under the species (*C. diurnum*) and note the manifestations (e.g., due to hypercalcemia) that may occur.

Night-Blooming Cestrum - The attractive lance-shaped leaves, the fragrant greenish-white to cream-colored tubular flowers, the clusters of white berries (lower left), and the enlarged berry and seed (left center) characterize this tropical plant.
**Solanum spp. - Nightshade Group**

*S. nigrum, S. americanum, S. ptycanthum* - black nightshade, deadly nightshade, nightshade

*S. tuberosum* - Irish or white potato.

*S. carolinense* - horse nettle, Carolina horse nettle, bull nettle, treedsalve, sandbriar, thread softly.

*S. elaegnifolium* - silverleaf nightshade.

*S. rostratum* - buffalo bur, Kansas or Texas thistle.

*S. dulcamara* - European bittersweet.

*S. gracile* - graceful nightshade.

*S. pseudocapsicum* - Jerusalem cherry, natal cherry.

*S. torreyi*

*S. triflorum* - cutleaf nightshade.

*S. villosum* - hairy nightshade.

*S. melangena* - egg plant.

*S. intrusum*

*S. aculeatissium (S. capsicoides)* - devil's apple, sode-apple, love apple.

*Lycopersicon* - tomato.

*S. malacoxylon* - (see Vitamin D containing plants).

<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><strong>Potato</strong> <em>(Solanum tuberosum)</em></td>
<td>Herbivores</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
</tr>
<tr>
<td><strong>Black nightshade</strong> <em>(Solanum nigrum)</em></td>
<td>Herbivores</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
</tr>
<tr>
<td><strong>Jerusalem cherry</strong> <em>(Solanum pseudocapsicum)</em> (may also contain cardiotoxic solanocapsine)</td>
<td>Herbivores</td>
<td>Minutes to hours</td>
<td>Hours to 3 days</td>
</tr>
<tr>
<td><strong>Tomato leaves, green fruit</strong> <em>(Lycopersicon)</em> (may also contain toxic amounts of nitrate)</td>
<td>Herbivores</td>
<td>Minutes to hours</td>
<td>Hours to 3 days; may also contain nitrate</td>
</tr>
</tbody>
</table>

Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)

**Family** - Solanaceae

**Images**

- *Solanum* spp. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Buffalo Bur *(Solanum rostratum)* - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at www.ivis.org.
**Geographical Location and Habitat**

- **S. nigrum.**
  - Maine to N. Dakota, south to Florida, Louisiana and Texas; Canada and Europe. Waste areas, cultivated fields, around homes, disturbed fields and pastures, moist, open areas in woodlands, loamy or gravelly soils, roadsides and streambanks.
- **S. americanum.**
  - Florida and Georgia, west to California and south through South America as well as north and west to southern British Columbia.
- **S. ptycanthum.**
- **S. carolinense.**
  - Massachusetts to Nebraska, south to Texas and Florida, some western states (southern California). Overgrazed pastures, cultivated areas.
- **S. eleagnifolium.**
  - Missouri to Texas and California and south into Mexico.
- **S. rostratum.**
  - North Dakota to Texas, westward and south into Mexico. Old fields, overgrazed pastures, roadsides.
- **S. malacoxylon.**
  - Ubiquitous in much of Brazil and Argentina; also in Hawaii; occurs especially in areas prone to flooding, and in pastureland.
- **S. dimidiatum.**
  - Grows in Texas, west of the Colorado River. Note: This is not the major river of the same name that runs through several western states.

**Description**

- **S. nigrum.**
  - Climbing perennial herb reaching up to 3 m tall, but usually 0.3 - 1 m tall, annual, erect. Leaves are alternate, simple or deeply lobed, wavy-toothed or oval- to lance-shaped, stalked and long, 3.8 - 10 cm. Flowers are white with large yellow anthers, which extend from the leaf axils in small drooping clusters with 2 - 20 blossoms. Flowers are small (0.6 - 1 cm across) with 5 white or pale violet petals. Fruits are round, 0.6 cm thick, purple-black when fully ripened, green when unripe, and contain many seeds.
- **S. carolinense.**
  - Perennial herb, 0.3 - 0.6 m tall, with yellow spines on the stems and simple, oblong, irregular or lobed leaves. Flowers are pale violet or white. Fruits are yellow berries about 1.2 cm in diameter.
- **S. eleagnifolium.**
  - Perennial, 0.3 - 1 m tall, with a white hairy stem, and simple, thick, lanceolate to linear leaves with short, stiff spines. The leaves are silvery white in color. Flowers are violet or blue, and fruits are yellow or orange berries. Plant has long creeping rootstalks.
- **S. pseudocapsicum.**
  - A shrub or potted plant growing up to 1.3 m tall, with dark green, shiny, waxy leaves, oblong in shape and 10 cm long. Flowers are white, in clusters, or alone, and 1.2 cm wide. Fruits are globular, 1.2 cm in diameter, scarlet or yellow, and resemble miniature tomatoes.
- **S. malacoxylon.**
  - A shrub, up to 1 - 1.5 m tall, smooth with sharp pointed, lanceolate somewhat fleshy leaves on comparatively long stems.
- **S. dimidiatum.**
  - Perennial, 1 m tall, with short, rounded, leaves of 15 cm in length. Fruit are pale yellow berries of ~3 cm in diameter.

**Toxic Principles**

- Many contain the steroidal glycoalkaloid solanine. Upon hydrolysis, a sugar and the alkaloid solanidine are recovered. The free (unconjugated) steroidal alkaloid (the aglycone) is the primary form acting on the nervous system.
- Other aglycones present may include dihydrosolanidine, tomatidine and strophanthidin. Toxic properties of these compounds are characteristic of saponins. Some plants may also contain saponins.
- Some of these plants also have cardiac effects, e.g., Jerusalem cherry (S. pseudocapsicum) contains an additional alkaloid, solanocapsine, which produces bradycardia. The plant may also irritate the skin.
- In some plants, atropine-like constituents predominate, e.g., potato (S. tuberosum), and some strains and stages of black nightshade (S. nigrum).
- **Solanum malacoxylon** contains toxic amounts of 1,25-dihydroxycholecalcified glucoside section on Vitamin D containing plants for
information on the toxic effects of this plant.

- *S. dimidiatum*
  - Toxic principle is unknown.

**Toxicity**

- Often poisoning occurs under conditions of overgrazing.
- Generally, the leaves and green fruits are toxic. The juice in the wilted leaves is especially toxic, and may be deadly if ingested. Many cases of poisoning have been reported as a result of eating green berries. Berries (green) have produced severe intestinal, oral and esophageal lesions in sheep. Cattle reportedly seek out the berries of *Solanum* and will eat the green plant, especially when other green forage is unavailable.
- Silverleaf nightshade (*S. eleagnifolium*) is exceptional in that the ripe fruit is more toxic than the green. *S. eleagnifolium* is toxic at only 0.1% of the body weight.
- Toxicity is not lost upon drying. Solanine content increases up to maturity.
- Solanine is reportedly destroyed by cooking except potatoes (see below).
- Potato (*S. tuberosum*) peeling contain the major portion of the toxic principle in the tuber, and leaves, sprouts, vines and especially sun-greened potatoes are toxic. Spoiled potatoes and peeling have also caused severe poisoning. Cooking does not appear to destroy all the alkaloids in greened potatoes. Toxicity may vary with the soil, climate and other variables. Animals may browse potato plants or eat sprouted potatoes, leading to problems. Potatoes containing over 0.02% of solanine are considered toxic to man. Several lethal toxicoses in human beings reported.
- Jerusalem cherry (*S. pseudocapsicum*) leaves and fruits have poisoned children, and may also cause dermatitis.

**Mechanism of Action**

- Solanine is a direct irritant of the esophageal and gastric mucosae.
- The steroidal alkaloids act as inhibitors of acetylcholinesterase although their potency in this regard, and thus the centrality of this mechanism is debated. Regardless; the alkaloids are clearly neurotoxic and often they cause ataxia and depression.
- Atropine-like alkaloids from some *Solanum* species competitively inhibit acetylcholine at muscarinic receptors.

**Susceptible Species**

Sheep, goats, calves, adult cattle, chickens, ducks, horses, rabbits, dogs, humans, swine (especially), and presumably other species.

**Signs**

- Clinical signs vary with the irritant effect caused by the intact glycoalkaloid or saponin, and the nervous effects of the alkaloid.
- Irritant effects include salivation, anorexia, severe gastrointestinal disturbances, with diarrhea that is often early and hemorrhagic.
- The nervous effects include apathy, drowsiness, depression, confusion, progressive muscular weakness, numbness, dilated pupils, trembling, labored breathing, nasal discharge, rapid heartbeat, weak pulse, bradycardia, CNS depression, and incoordination, often accompanied by paralysis of the rear legs. Coma may occur without other nervous signs.
- High doses may cause intestinal stasis and constipation.
- Hemolysis and anemia, possibly a result of saponins have been reported.
- Renal failure has been reported in severe cases.
- Terminal signs include unconsciousness, shock, paralysis, coma, circulatory and respiratory depression, and death.
- The course varies from sudden death to a course of 3 - 4 days which may terminate in death or recovery. In less acutely poisoned animals, there may be yellow discoloration of the skin in unpigmented areas, weakness, incoordination, tremors of the rear legs, anemia, rapid heart rate and bloat.

**Lesions**

- No lesions occur in some cases involving sudden death from large doses. In other animals, there may be edema around the kidneys, clots around the kidneys, and possibly pale kidneys which exhibit tubular necrosis when examined histologically. Gastroenteritis may
be minimal or may include hyperemia, hemorrhage and ulceration of the alimentary tract. The liver may be congested and the gallbladder distended. There is sometimes edema of the ventral body wall and congestion and emphysema in the lungs. Hemorrhage and congestion may also occur in the heart and spleen.

- *S. dimidiatum* is unique among Solanaceae in causing necrosis of Purkinje cells of the cerebellum.

**Treatment**

- Establish respiration, induce vomiting unless contraindicated, activated charcoal, saline cathartic.
- Symptomatic and supportive treatment. Maintain body fluid and electrolyte balance.
- Dermatitis may be relieved by washing with soap and water and application of corticosteroids.
- When life-threatening, atropine-like poisoning is suggested based on clinical signs, consider physostigmine therapy (as for atropine ingestion; see Introduction to Anticholinergic Agents section). If signs suggesting cholinesterase inhibition predominate, consider cautious (!) treatment with atropine.
- Cattle surviving 24 hours will generally recover.

**Prevention**

- The pasture should be mowed before the seeds ripen to control propagation of the weeds. Keep animals out of areas with heavily concentrated weeds, especially if forage is not abundant. Hungry animals should not be allowed to graze areas where an abundance of silverleaf nightshade is growing. Remove green parts of potatoes before cooking, eat only ripe tubers.
- Herbicides are sometimes used to help control nightshades.
- When in hay and animals are preferentially eating the other plants, consistent overfeeding of the hay and daily removal of the "wasted" (uneaten) poisonous plants may sometimes be an economic (but not risk-free) necessity.

**Note**

- Some of the lesions of *Solanum* toxicosis are occasionally similar to those of *Amaranthus retroflexus* (pigweed) poisoning.
- Do not confuse deadly or bittersweet nightshade (*S. dulcamara*) with climbing bittersweet (*Celastrus scandens*).
Potato - The pinnelely divided leaves, the white or bluish flower (upper left), the yellowish or green berries (lower right), and sprouted tuber (lower left) are characteristic of this important, sometimes poisonous, food plant.
Jerusalem-Cherry - Note the oblong, wavy-margined leaves, the white flowers (enlarged, lower left), and the attractive berries (enlarged, lower right) and seeds (enlarged, lower center) of this ornamental plant.
Horse Nettle
(Solanum Carolinense)

European Bittersweet
(solanum Dulcamara)
Introduction to Muscarinic Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
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</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>All species</td>
<td>Minutes</td>
<td>Hours; rarely lethal</td>
</tr>
<tr>
<td>Arecoline</td>
<td>Dogs, cats</td>
<td>Minutes</td>
<td>Hours; rarely lethal</td>
</tr>
<tr>
<td>(obsolete drug formerly used to treat small animals for tapeworms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methacholine</td>
<td>All species</td>
<td>Minutes</td>
<td>Hours; rarely lethal</td>
</tr>
<tr>
<td>Carbachol</td>
<td>All species</td>
<td>Minutes</td>
<td>Hours; rarely lethal</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>All species</td>
<td>Minutes</td>
<td>Hours; rarely lethal</td>
</tr>
</tbody>
</table>

Muscarinic Receptors

- Postganglionic parasympathetic neuroeffector junctions.
- Parasympathetic cardiac, parasympathetic smooth muscle, and exocrine gland innervation.
- Also present at some smooth muscle (e.g., arterioles) sites without cholinergic innervation.
- Cholinergic neuroeffector junction of the sympathetic nervous system (e.g., at ganglion).
- Parasympathomimetic.

Acetylcholine Receptors

Nicotinic
Agonists: ACh, nicotine
Non-depolarizing Blocker: Curare

Muscarinic
Agonists: ACh, muscarine
Nondepolarizing Blocker: Atropine

This section refers only to muscarinic agents. Recall, however, that there are 2 kinds of acetylcholine receptors: sites of action of muscarinic vs. those of nicotinic alkaloids. The synaptic endings shown both release acetylcholine (ACh). The postsynaptic membrane on the left responds both to ACh and to nicotine but not to muscarine. The response of the receptors can be blocked by curare. The receptors are described as nicotinic. The postsynaptic membrane on the right responds to ACh and to muscarine but not to nicotine. The response can be blocked by atropine. The receptors are called muscarinic.

Sources of Muscarinic Toxicants

- Muscarinic Alkaloids.
  - **Muscarine** has been used to identify muscarinic receptors—not used as a drug. Originally isolated from *Amanita muscaria*; although usually not the primary toxic principle.
  - **Pilocarpine** is isolated from the Brazilian shrubs, *Pilocarpus jaborandi* and *P. microphyllus*. It is used as a miotic. Can have systemic effects, e.g., anomalous cardiovascular responses. Used therapeutically for glaucoma and other ophthalmic conditions requiring miosis. Especially effective at stimulating exocrine gland secretions.
  - **Arecoline** is the primary alkaloid from *Areca catechu*, or betel nut (East Indies).
    - Potent stimulant of gastrointestinal motility (e.g., has been used for tapeworm removal).
    - Acts to a lesser extent at nicotinic receptors.
Muscarinic Choline Esters.
- Acetylcholine itself.
- Methacholine.
- Carbachol
  - Especially GI and urinary tracts.
- Bethanechol

Signs

- Muscarinic Signs.
  - Colic, can be severe, diarrhea, vomiting.
  - Visual disturbances, miosis.
  - Hypotension and bradycardia (mediated via vagus). Severe bronchospasm and bronchial secretions can cause death.
  - Shock.
  - Exocrine secretions including salivation and lacrimation.
  - Exposure to arecoline or systemic exposure to pilocarpine is contraindicated in animals with heart failure, depression, or spasmodic colic, as well as during gestation.

Treatment

- Atropine-Repeat as needed. Dose to effect as for organophosphorus insecticide toxicosis.
- Evacuate gastrointestinal tract if oral exposure has occurred.
- Activated charcoal.

Muscarinic - Histaminic Mushrooms

Mushrooms

*Boletus eastwoodae, Boletus luridus, Boletus satanas,* and possibly other species of *Boletus* with red pore mouths. *Clitocybe cerussata, var. difformis, Clitocybe dealbata, Clitocybe illudens, Clitocybe rivulosa, Inocybe fastigiata, Inocybe geophylla, Inocybe lilacina, Inocybe patuoillardi, Inocybe pudica,* and possibly others.

Images

- *Clitocybe cerussata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- *Clitocybe dealbata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- *Clitocybe illudens* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- *Clitocybe rivulosa* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- *Inocybe fastigiata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
Pharmacology

L(+)-muscarine and other less potent cholinergic compounds. Because of its quaternary configuration, muscarine does not cross the blood brain barrier to the central nervous system. Therefore, the cholinergic effect is entirely peripheral. Some of the muscarinic compounds have more of a histaminic effect with flushing, hypotension and asthmatic wheezing.

Signs

Onset within 30 - 120 minutes. Excessive perspiration (humans), salivation, and lacrimation, miosis, blurred vision, bradycardia, and increased peristalsis with crampy abdominal pain; and watery stools. These are followed by reduced blood pressure, pulmonary congestion and asthmatic wheezing.

Note - The perspiration-salivation-lacrimation combination reportedly does not occur in other types of mushroom poisoning.

Toxicity

Fatality rates for poisoned humans range from 6 - 12%. Most deaths occur in children with cardiac or pulmonary disease.

Diagnosis

Muscarine has been detected in urine and can be used for confirmation of this type of poisoning. Effective treatment should be instituted on the basis of clinical signs and history before any laboratory work is available. Response to therapy helps to confirm the diagnosis.

Treatment

- Prevention of absorption:
  - Emesis should be initiated unless the patient is comatose, convulsing, or has lost the gag reflex.
  - If contraindications to emesis exist, intubation should precede gastric lavage.
  - Emesis may not be of further value if the animal has already vomited repeatedly.
  - Activated charcoal is recommended at 5 - 10 times the estimated ingested dose or 2 g/kg in a water slurry.
  - Sodium sulfate 250 - 500 mg/kg/orally as a cathartic in a 20% or more dilute aqueous solution.
- Atropine.
  - Should be administered if life-threatening cholinergic symptoms exist. An atropine test dose of 0.05 mg/kg should be administered. If the patient is poisoned, no signs of atropinism (e.g., tachycardia, dry mouth) will develop; and the atropine dose may be increased and repeated as needed. The endpoint is cessation of excessive bronchial secretions, and especially ease of breathing, not dilatation of pupils and not cessation of salivation.
  - Supportive care with intravenous fluids may be necessary.

<table>
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<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, horses, sheep</td>
<td>Hours</td>
<td>Up to 3 days; unlikely to be lethal</td>
</tr>
</tbody>
</table>

Slaframine

- Slaframine or "slobber factor" is an indolizidine alkaloid mycotoxin produced most often in red clover *Trifolium pratense* infected by the fungus *Rhizoctonia leguminicola*, which is the cause of "black patch" of this and other legumes. The toxin is sometimes also
present in other legume forages contaminated by this mold.
- The parent compound, slaframine, has no activity but is transformed in the body to a quaternary amine (ketoimine) which is chemically (and to some degree physiologically) somewhat similar to acetylcholine.
- *R. leguminicola* can survive over 1 - 2 seasons in red clover seed.
- Moist weather precedes the occurrence of "slobber factor" in toxic concentrations.
- The production of slaframine is decreased at temperatures over 25 °C.
- No resistant strains of red clover have yet been found.
- Occasionally slaframine may be produced in other types of legume forages.
- The toxin is a constituent of the fungus rather than an "exotoxin".

**Mechanism of Action**

- Cholinergic stimulation of exocrine glands (actually mimics ACH at the receptor, rather than causing ACH release).
- No effect on ganglionic transmission, peripheral blood flow or neuromuscular transmission.
- At reasonable doses, there is no change in heart rate, respiration, or blood pressure.

**Susceptible Species**

Toxicosis is most commonly reported in cattle, horses, and sheep. Goats may also be affected, but other species have been demonstrated to be susceptible including: swine, chickens, guinea pigs, rats, and mice.

**Toxicity**

In LA, signs begin after 5 - 15 # of affected red clover has been eaten.

**Signs**

- May occur 30 - 60 minutes after first consumption of affected hay. Some sources suggest that they generally occur after a latent period of 4 - 6 hours postingestion. Clinical signs intensify up to 24 hours postexposure, and condition usually resolves within 96 hours after the last feeding of the contaminated hay.
- Clinical signs may last from 6 - 8 hours in small laboratory animals.
- Excessive salivation is usually the first sign.
- Lacrimation, rarely severe.
- Anorexia (sometimes animals refuse to eat more of the contaminated forage).
- Diarrhea, sometimes watery.
- Frequent urination.
- Bloat.
- Decreased milk production.
- Abortion.
- Stiffness.
- Death has been reported in cattle.
- The principle economic losses are associated with reduced production and feed replacement costs.
- Horses with significant toxicoses have been observed to salivate, so severely, that after being tied to a post for a few minutes a puddle of saliva accumulates in the soil beneath their heads. These horses were consuming a stemmy, black hay, barely identifiable as to the plants contained but identified as red clover hay. In spite of the severe salivation, the horses were being ridden repeatedly on a horse-for-hire basis and did not appear to experience other adverse effects upon casual observation.
Lesions

- Guinea pigs:
  - Experimentally dosed animals had pulmonary hyperemia, edema, and emphysema. Liver and kidney congestion.
  - Tracheal submucosal eosinophilia was noted but its significance and consistency are not known.
- Pregnant rats:
  - Uterine hemorrhage and abortion.
- Pregnant cattle and horses:
  - Occasional abortions reported.

Diagnosis

- SLUD: salivation, lacrimation, urination, defecation (all muscarinic signs), but may see only salivation.
- Usually red clover in the diet is second cutting hay.
- Presence of dark brown mycelium in the hay or on the pasture plants.
- The mycelium is very much larger than most other fungi.
- Confirm by identifying the *R. leguminicola* in the forage or by bioassay.
- May get false negatives from attempts to culture the fungus.

Bioassays:

- Guinea pig bioassay (feed test).
  - Finely grind red clover, especially stems, and mix with equal parts of ground guinea pig pellets. Feed at least 1 week and check daily for salivation.
- Guinea pig bioassay (fungus test for toxigenic potential).
  - Isolate *R. leguminicola*, and cultivate on extracts of red clover not other substrates. Force feed mycelium to guinea pigs.
  - Salivate in 60 minutes.
  - Note - culture filtrates are not toxic.
  - Alternatively, can extract mycelium from fungus with chloroform at a pH between 7 and 10 (higher will hydrolyze slaframine), dry, dissolve in saline, adjust pH to neutrality and inject guinea pig IP. A positive test result is comprised of salivation in 10 - 30 minutes.
- Bovine (feed test).
  - Grind up and administer into a fistulated cow.
  - Salivation, epiphora, diarrhea and/or other cholinomimetic signs comprise a positive response.

Direct identification of slaframine in toxic hay is possible:

Confirmation of slaframine can be obtained by submitting suspected hay or legumes in pastures to the Diagnostic Laboratory at the College of Veterinary Medicine of Iowa State University at Ames, IA, USA.

Treatment

- Remove from source. Most animals will recover.
- Will take 2 - 3 days for affected animals to respond.
- Symptomatic treatment in severely affected animals.
  - Atropine not very effective unless given before slaframine.
  - Therefore slaframine must have greater affinity for receptor than atropine.
  - Antihistamines reported to be effective.

Note

*R. leguminicola* may also produce swainsonine, which is structurally - somewhat similar to slaframine. Swainsonine is the toxic constituent of "true locoism" in *Astragalus* and *Oxytropis* spp. Whether the amounts present in red clover are sufficient to cause clinical or histologic changes similar to those in true locoism seems unlikely.
3. Inhibitors of Cholinesterase

**Organophosphorus and Carbamate Insecticides**

<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 Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organophosphorus insecticides and avicides</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Days to 4 weeks; often lethal</td>
<td></td>
</tr>
<tr>
<td>Carbamate insecticides</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 1 day; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Organophosphorus (OP) insecticides are often referred to as organophosphates, which is actually a misnomer (they are not salts).

- Most are applied to surfaces of plants, animals, soils, or household floors, etc.
- Others are systemics:
  - Absorbed via any route by plants or animals and distributed through the organism on which the insect pest feeds.
- The most prevalent and toxic chemical warfare agents are potent OP compounds (soman, sarin, tabun). These compounds are not used as insecticides.

Carbamate insecticides, which are derivatives of carbamic acid are used for similar surface applications.

- The original carbamate, physostigmine, is a plant alkaloid, derived from the "ordeal bean" (see Introduction to Anticholinergic Agents section for therapeutic uses of physostigmine).

Both OP and carbamate groups contain members comparatively low in toxicity and others which are extremely poisonous.

**Sources**

**Feed-Related Problems:** (80% of all exposures in food animals).

- Misidentification of granular pesticides as vitamin or mineral supplements.
  - Aldicarb granules are black to grey outside; beige inside.
- Adjacent storage of feed ingredients and pesticides.
- Use of vehicles to transport pesticides prior to transporting feed.
- Accidental or excessive application to forage crops.
Other Sources

- Miscalculation of dosage during spraying, dipping, oral dosage.
- Exposure of animals to products intended for other species (e.g., cats treated with dips for dogs).
- Exposure of pets to insecticidal products applied to the home.
- Use of insecticides on stressed animals.

Mechanism(s) of Action

- Acetylcholine (ACH) is the mediator at junctions including those between:
  - Preganglionic and postganglionic neurons in both parasympathetic and sympathetic nervous system.
  - Postganglionic parasympathetic fibers and smooth muscles or glands.
  - Motor nerves and skeletal muscles.
  - Some neuron to neuron junctions in the CNS.

- Acetylcholinesterase (ACHE) also known as true cholinesterase is the enzyme that rapidly hydrolyzes ACH at these locations.
  - Red blood cells contain primarily ACHE and plasma contains pseudocholinesterase. The actual physiological purposes of the enzymes located in blood are unknown.
  - During its action, acetylcholinesterase is very temporarily bound to the acetyl and choline ends of the molecule until hydrolysis and release of choline and acetate occurs. Prior to the release of the acetate (which is released last), the enzyme is, for an instant, "acetylated".

- Binding of acetylcholinesterase by a carbamate insecticide is generally followed by hydrolysis of the insecticide, but the enzyme remains temporarily carbamylated and thus inhibited. The binding, and associated inhibition, is generally reversible, but often lasts long enough to allow clinical signs and sometimes death to occur.
- Organophosphate and carbamate insecticides competitively inhibit both acetylcholinesterases and pseudocholinesterases.
- The binding of acetylcholinesterase by different organophosphorus inhibitors varies somewhat in affinity and reversibility. After binding, the enzyme is "phosphorylated", and thus inhibited. Generally speaking, much of the binding of ACHE by an OP is regarded as "irreversible".
- With some of the OP compounds, after binding to acetylcholinesterase, a chemical change in the OP takes place which significantly strengthens the attachment of the phosphorus to acetylcholinesterase. This is referred to as "aging" of the insecticide, and it occurs to different degrees and at different rates with various OPs. After aging, treatment by oximes is not effective in reversing the binding of the OP.
- Some OPs (especially those with a -P=S moiety) require metabolic oxidation to form a -P=O before they effectively inhibit acetylcholinesterase.
As a result of phosphorylation or carbamylation, the acetylcholinesterase enzyme ceases its normal function and acetylcholine concentrations at neuroeffector sites build up, resulting in continuous stimulation of nervous, glandular, or muscular receptors.

Different cholinesterase inhibitors have additive effects.

Phenothiazine and derivatives as well as other agents including some quaternary ammonium bases may also inhibit cholinesterases, potentiating the toxicity of the insecticide.

Cholinesterase inhibitors potentiate succinylcholine by inhibiting pseudocholinesterase, by which it is normally hydrolyzed. This can produce a profound increase in the intensity and duration of succinylcholine-induced respiratory paralysis.

Death due to OP or carbamate toxicoses is usually due to one or more of the following effects:

- Increased respiratory tract secretions and bronchiolar constriction with hypoxia aggravated by bradycardia.
- Respiratory depression from nicotinic stimulation to the point of paralysis.
- Respiratory paralysis from CNS depression due to central effects of the insecticide (may be the primary cause of respiratory failure in some species).

Signs

- 3 categories of effects occur in poisoned animals: muscarinic, nicotinic, and central nervous system effects.
- Muscarinic:
  - Salivation.
  - Gastrointestinal hypermotility, pain, vomiting, and diarrhea.
  - Lacrimation.
  - Miosis (or mydriasis perhaps attributable to epinephrine release).
  - Dyspnea (bronchial secretion, constriction) and resultant cyanosis.
  - Micturition.
  - Bradycardia (or tachycardia perhaps attributable to epinephrine release).
- Death may result from hypoxia, which results from bronchial secretions, bronchoconstriction, and an erratic, slowed heartbeat.
  - Horses - colic, abdominal pain, salivation, severe diarrhea (often watery), dehydration.
- Nicotinic:
  - Stimulation of skeletal muscles:
    - Twitching of facial muscles, eyelids, tongue, and eventually the general musculature.
    - Generalized tetany.
    - Subsequent weakness and paralysis, possibly respiratory paralysis and death.
- Central nervous system:
  - Vary with species: severe CNS depression common in any species.
    - Food animals - often exhibit hyperactivity.
      - Rarely if ever, seizure.
    - Dogs and cats - occasionally seizure.
      - Hyperactive.
      - Hyperreflexive.
    - Centrally mediated respiratory paralysis (may be lethal).
- Specific OP characteristics.
  - Coumaphos, a systemic, may cause a syndrome with a slower onset, muscarinic and nicotinic signs including tetany and seizure prior to death.
  - Crufomate (Ruelene)-another systemic causes early rigidity and ataxia and later depression and muscarinic effects.
  - Chlorpyrifos (Dursban 44)-pour on in bulls and exotic beef breeds.
• Maximal (topical) dose (16 ml) is for 800# (animals larger than 800# all get same dose as an 800# animal). Bulls of 2200# may die from the 800# dose (7 mg/kg).
• Signs of chlorpyrifos toxicosis in cattle include anorexia, diarrhea, rumen stasis with fluid accumulation, dehydration, and death. Effects in topically exposed cattle may persist for days to a few weeks.
• Cats: minimum lethal dose (oral) in cats (a highly sensitive species) of approximately 40 mg/kg.
  • Lethal toxicosis often results from the inappropriate use of dog flea dips containing chlorpyrifos on cats.
  • Signs in cats include: depression (occasional aggression), anorexia, salivation, vomiting, diarrhea, ataxia, tremors, and dyspnea. The depression and anorexia in topically exposed cats may persist for days to a few weeks. Orally exposed cats may recover in a few days.
  • May produce delayed neuropathy, at least in heavily exposed cats.
• Ronnel-weakness in rear limbs, dragging of hind feet when walking, may last for up to several weeks.
• Diazinon causes problems, especially in small animals and birds. Commonly used on lawns. It has been recently banned in golf course use.

Lesions

• Nonspecific.
• Salivation.
• Bronchial secretion or pulmonary edema.
• Occasional hemorrhages in gastrointestinal tract serosa and mucosa.

Residues

• Vary with the specific compound, degree, and route of exposure.
• Generally the carbamates cause comparatively little concern in the overall environment (on a broad scale) or in animal tissues, although aldicarb can be a problem in water, including ground water, and on vegetables (aldicarb in watermelons, 1985 in California).
• The OPs tend to be much less persistent than the organochlorine insecticides.

Diagnosis

• Excessive exposure and appropriate clinical signs.
• Reduced whole blood cholinesterase activity may suggest exposure to an organophosphate or carbamate and, although, not a conclusive test, should be performed on animals presented alive. In most species whole blood cholinesterase is considerably less sensitive than pseudocholinesterase. Therefore, depression of the activity of whole blood cholinesterase is more indicative of serious exposure or toxicosis than plasma pseudocholinesterase. Conversely, plasma pseudocholinesterase is a more sensitive test for detecting exposure than whole blood cholinesterase. It is possible to have no plasma cholinesterase activity detected in animals exposed to therapeutic (parasiticidal) amounts of OPs.
• In most species, the red blood cells contribute the major fraction of the activity in total blood cholinesterase.
• In most instances, the whole blood cholinesterase values of lethally poisoned animals fall below 25% of control values.
• In the cat, plasma pseudocholinesterase accounts for the vast majority of whole blood cholinesterase. Thus, the cat is very sensitive to depression of the total blood activity, even after exposures to amounts well below those capable of causing clinically evident toxic effects.
• Brain cholinesterase is very important in assessing the probability of poisoning in dead animals (obtain as soon as possible-right away after death, freeze, ship so that specimen remains frozen).
• Because the incubation time allows for decarbamylation, the Michel method of cholinesterase analysis may give false negative (false normal) values for carbamate toxicoses.
• Testing blood or homogenized brain tissue for cholinesterase activity at several times before and during a period of laboratory incubation can be used to differentiate an OP toxicosis (minimal or no regeneration of activity) from a carbamate (substantial regeneration of activity and potentially even full toxicosis recovery to normal values).
• Internal organs (e.g., liver) of poisoned animals may contain detectable residues of organophosphorus insecticides. Also, most of the compounds (OPs and carbamates) may be found in significant concentrations in skin and subcutaneous tissue after topical exposure.
• Stomach or rumen contents are often important in confirming diagnoses after oral exposure because the insecticides are often detected in these samples (ship frozen).
• There is a field screening test to detect cholinesterase inhibitors in air, water, soil, crops, spills, surfaces, solvents and other samples (Neogen Corporation, Lansing, MI).
• Test dose of atropine: try a preanesthetic dose of atropine and, if normal atropinization occurs at this dose (normal extent and duration of rapid heart rate, dry mouth and mydriasis), it tends to rule out poisoning from a cholinesterase inhibitor.
Treatment
Urgent

- Very early, emetics (only for very recent exposures; never when contraindicated and never when constant monitoring will not be undertaken).
- Activated charcoal (for any recent oral exposure) administered with appropriate precautions to avoid aspiration.
- Thoroughly bathe with detergent all animals exposed topically-taking care to avoid exposure of human skin. Use thick rubber gloves, plastic aprons, etc.
- Atropine sulfate (generally avoid use of charged agents, such as atropine methylnitrate or glycopyrrolate, which do not effectively enter the central nervous system).
  - Atropine sulfate-dosages higher than preanesthetic doses are routinely required for acute toxicoses (OP or carbamate).
  - Small animal products may contain atropine sulfate at 0.5 or 0.54 mg/ml; large animal products may contain 2 or 15 mg/ml.
  - May want to avoid atropine sulfate altogether in horses due to gut stasis, (except with life-threatening pulmonary or cardiac effects). When used in horses, atropine is added to fluids and administered IV while ausculting the abdomen. Administration is stopped prior to a reduction (to less than normal) in gastrointenstinal sounds.
  - Suggested dose cattle 0.2 - 0.5 mg/kg. One-third of dose administered IV, the remainder given SC or IM.
  - Atropine is repeated judiciously as needed; but avoid gut and rumen atony. May be required at 4 - 8-hour intervals.
  - Suggested dose SA and birds 0.2 mg/kg. Some rabbits have atropinase and may require higher dosing, begin at 1.0 mg/kg but may need to increase to 10 mg/kg.
  - In all cases, subsequent doses of atropine should depend on the reappearance and severity of clinical signs. Clinical signs to use for monitoring include degree of respiratory distress, cyanosis, and heart rate. Effects such as miosis and salivation, which are not of concern in survival, are not used as therapeutic end points for atropine administration.
- Oximes.
  - Protopam (2 PAM), Pralidoxime hydrochloride, or TMB-4 act on the OP-ACHE complex to free the enzyme to resume its normal function if aging has not occurred and to enhance excretion of the insecticide. Not clearly proven of any benefit in carbamate toxicoses. Based on early, but since disputed data, it is often stated that 2-PAM is contraindicated in carbamate poisoning. However, when in doubt as to whether an insecticide poisoning is due to an OP or a carbamate, but signs suggest a cholinesterase inhibitor, an oxime should be used. Oximes are usually repeated BID. Protopam is given IM or IV at 20 mg/kg BID and continued, for days to weeks if necessary, until nicotinic signs resolve. If no response is apparent after 4 doses, the value of additional 2-PAM is in doubt and use of the drug should probably be discontinued. Cattle and horses can be dosed at 10 - 20 mg/kg.
  - Topically administered organophosphorus insecticides may be absorbed into the skin and/or subcutaneous fat before systemic distribution. Thus, absorption from these sites (skin, fat) may occur over several days time, and "aging" of the insecticide on the cholinesterase enzyme may not have occurred so that oximes may still be of benefit in these cases-even days after the initial exposure.
  - 2-PAM is generally of low toxicity. Overdoses can be associated with tachycardia, cardiac arrhythmias.
  - The maximum shelf-life of reconstituted 2-PAM is two weeks.
Artificial respiration may be needed to counteract respiratory paralysis. Severe bronchospasm may be responsive to theophylline therapy. Older literature, however, suggests theophylline may increase occurrence of seizures in OP toxicosis. It is essential to avoid hypoxia.

Scopolamine maybe of value when severe CNS depression is not responsive to atropine therapy, but this is not widely accepted.

Diphenhydramine has been recommended at 1 - 4 mg/kg per os every 6 - 8 hours to help control persistent nicotinic signs.

Seizures may be controlled with diazepam or barbiturate anticonvulsants.

Systemic acidosis may complicate OP or carbamate poisoning. Counteracting respiratory failure with atropine and/or assisted ventilation are recommended for respiratory acidosis. Sodium bicarbonate administered at an initial dose of 5 mg/kg IV can be used to correct metabolic acidosis. Subsequently, IV doses at 1 - 3 mEq/kg may be required. Monitor acid base status.

Animals should be monitored for the development of chemical pneumonitis due either to aspiration of hydrocarbon solvents (when such formulations are ingested) or for aspiration of gastric contents.

Stress of OP or carbamate toxicosis may predispose animals to secondary clinical problems: e.g., hemobartonellosis, reported in OP-poisoned cats.

If prolonged administration of high doses of atropine is anticipated, it is best to avoid preparations containing benzyl alcohol preservatives in species/ages (e.g., cats and all neonates) susceptible to benzyl alcohol-related toxicosis (see section on Benzyl alcohol).

**Delayed Neurotoxicity (Neuropathy)**

Certain OPs may cause a polyneuritis with paresis or paralysis primarily of the hindlimbs with degeneration of axons and myelin in the medulla, spinal cord, and peripheral nerve. This effect is not caused by acetylcholinesterase inhibition. One should be aware that for at least a few OPs including EPN, animals surviving acute poisoning as a result of therapeutic intervention may exhibit delayed neuropathy beginning a few weeks after the acute syndrome. Certain OPs, almost nontoxic with regard to acute poisoning, readily produce delayed neuropathy at low, otherwise non-toxic dosages. Most new OPs are evaluated in hens (the preferred test animal) for their ability to cause delayed neuropathy prior to marketing. This is discussed further under the heading "Toxicants Causing Paralysis".
**Anabaena flos-aquae - Blue-Green Algae**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th><strong>Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</strong></th>
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<td>All species</td>
<td>Minutes to hours</td>
<td>Days; often lethal</td>
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**Images**


**Habitat**

Warm, sunny weather generally precedes a "bloom" of blue-green algae (also called cyanophytes or cyanobacteria). Usually, significant growth occurs in ponds or lakes which accumulate runoff from fields that are heavily fertilized or that receive the runoff from lots or pastures bearing significant numbers of animals. An abundance of phosphorous in the water usually accompanies blooms. Poisoning is most likely when animals have access to the water in an area of a wind-concentrated bloom.

**Description**

- Macroscopically blooms consist of a "scum" on top of water, blue, blue-green or green in color. Has no macroscopic filaments or other organization.
- Microscopically chains of cells including primarily vegetative cells sometimes with lesser numbers of spores and/or heterocysts. Cells are approximately the size of erythrocytes.

**Anabaena flos-aquae and A. spiroides var. crassa Lemm.**

Note - *A. flos-aquae* can also take this form.

**Toxic Principles**

- **Anatoxin-a**: a nicotinic depolarizing alkaloid neurotoxin is produced by some *A. flos-aquae* and some *Oscillatoria aghardii* blooms. Extremely potent and fast acting.
- Both *Oscillatoria* and less often *Anabaena* may produce algal peptide hepatotoxins (see Microcystins).
- **Anatoxin-a(s)**: the only known naturally occurring organophosphorus cholinesterase inhibitor: (s stands for salivation) is produced by some *A. flos-aquae* blooms.
- May also produce saxitoxin or neosaxitoxin. These act by blocking sodium channels. These toxins also cause paralytic shellfish poisoning.
Signs

- Anatoxin-a poisoning is similar to succinylcholine overdose. Animals may show rapid onset of rigidity and muscle tremors, then paralysis, cyanosis, and death due to respiratory paralysis. The onset of death may occur very rapidly. For example, when a bloom containing anatoxin-a was present in a South Dakota lake in early September 1985, a dog jumped in the water, swam out, but died before it could swim back to shore. The dog had apparently swallowed a small amount of the algae.
- Anatoxin-a(s) toxicity results in cholinesterase inhibition and thus a build up of acetylcholine which causes excessive salivation, gastrointestinal hypermotility, diarrhea, urination, and (at least in mice) an excessive amount of ocular mucus production. In lethal cases, however, the nicotinic effects of this cholinesterase inhibitor are also seen and may include tremors, incoordination, paresis, paralysis, and terminal respiratory paralysis. Note in anatoxin-a(s) toxicity, retinal and brain cholinesterases are not inhibited, as it appears that the toxin cannot cross the blood brain barrier (BBB). The only centrally mediated signs are likely to be due to terminal hypoxia.
- Pigs and dogs are extremely sensitive to oral exposure. Ducks are of intermediate sensitivity. Cattle and lab rats are relatively resistant to orally administered anatoxin-a(s) containing algae, but these species are sensitive to parenterally administered lysed algae.

Lesions

- Algae-associated discoloration of hair and skin indicates exposure.
- Algae may or may not be evident in the gastrointestinal tract.
- Anatoxin-a toxicity produces no lesions.
- Anatoxin-a(s) toxicity causes diarrhea, salivation, excessive urination, and possibly a Sticky mucoid ocular discharge, evidence of which may be found on examination of the animals prior to or at necropsy.

Diagnosis

- The principle criteria for tentative diagnosis include ingestion of a significant amount of a blue-green algae and appropriate clinical signs.
- Initial microscopic examination of bloom material revealing the appropriate chains of algal cells increases the assurance of the diagnosis.
- In anatoxin-a(s) toxicity, there are depressed blood, plasma, and (in lethal cases) skeletal muscle cholinesterase activities with normal retinal and brain cholinesterase activities.
- For lethally poisoned animals, a complete necropsy should be used to rule out other causes and, in the case of hepatotoxin, to reveal the appropriate gross and histologic lesions.
- The Illinois CVM toxicology laboratory can arrange for analysis of stomach contents and algal bloom material for the hepatotoxin and for anatoxin-a. At this time, there are no analytical methods available for anatoxin-a(s).
- Confirmation of algal species is also dependent upon further examination of the algae. Kits to obtain appropriate algal specimens may be obtained from Dr. Wayne Carmichael, Department of Biology, Wright State University, Dayton, Ohio. In cases of acute toxicity, the specimens often can be collected and sent to Dr. Carmichael for organism culturing (small amount of "scum" added to bacterial transport media, refrigerated), organism identification (small amount of "scum" in an equivalent of 10% neutral buffered formalin), toxin analysis (2 L concentrated "scum", frozen), and when necessary, toxin bioassay using mice.

Treatment

- Avoid further exposure by fencing off contaminated ponds and lakes, as well as streams emanating from them. It has been theorized that, immediately after treatment with copper sulfate, an algal bloom may be of increased toxicity due to cell breakdown and a greater access to the toxin(s) present. This now seems unlikely in the case of the hepatotoxin but may be true for the neurotoxins.
- For apparent anatoxin-a poisoning, the rapidity of onset may make treatment impossible. If consumption has just occurred, measures to evacuate the gastrointestinal tract, bind the toxin (activated charcoal is likely to be benefit), and maintain respiration (artificial respiration) may be needed. Without additional therapy to remove the algae or bind the toxins, artificial respiration (for many hours) may not do anything more than prolong the onset of death. Whether the detoxification measure will be of benefit is not yet proven but seems plausible.
- For apparent anatoxin-a(s) toxicity, atropine may be effective (take care using in horses to avoid gut stasis and associated colic, which can be severe). Employ measures to terminate toxin absorption as described for anatoxin-a. Artificial respiration may also be of value, although the effects of the toxin are relatively persistent. There is no data to indicate a need for oxime therapy for anatoxin-a(s)-poisoned animals.
- For hepatotoxin poisoning, prognoses are poor in severely affected animals. Combatting shock and hemorrhage with fluids and blood are clearly indicated as is dextrose if hypoglycemic and measure to counteract hyperkalemia (if present), but severe liver damage may often preclude an uneventful recovery. Regeneration of hepatocytes in sublethal toxicosis has, however, been documented in mice.
Careful collection of a dense portion of an algae bloom is mandatory: collection of filamentous algae or other plants, or water containing little algae is not likely to be toxicologically meaningful.

Thoroughly mix algae and divide into at least 5 portions

Examine immediately under light microscopy for algal identification.

Fix cells in an equal amount of 10% neutral buffered formalin for identification at a later time.

Submit 2 L of frozen, concentrated algal bloom material to be freeze-dried for toxin analysis (see below*)

Refrigerate and submit for culture if highly toxic (do not freeze).

At veterinary facility or when fresh algae is hand delivered to a diagnostic laboratory, centrifuge at 9500 g for 10 minutes.

Cells at bottom of centrifuge tube. Decant water.

Freeze and thaw or sonicate to rupture (faster but not as thorough as freeze and thaw).

Centrifuge and collect supernatant.

Bioassay 1.0 ml i.p. into mouse.

Hepatotoxin present: death usually within 3 hours; liver weight (as %b.w.) increased by 60% or more.

Neurotoxin present: death usually within 30 minutes, often faster; no increase in liver weight, nervous signs.

*Request analysis of freeze-dried algae for peptide hepatotoxins

Anabaena only.

Profuse salivation and lacrimation.

Submit brain and blood for cholinesterase activity; if a cyanobacterial cholinesterase inhibitor such as anatoxin-a(s) is present, brain activity will be normal and blood activity will be depressed--no acceptable methods for toxin analysis yet available.

Aphanizomenon spp.

No profuse salivation or lacrimation

*Request analysis of freeze-dried algae for anatoxin-a saxitoxin & neosaxitoxin

*Request analysis of freeze-dried algae for saxitoxin or neosaxitoxin by HPLC.
4. Toxicants with Nicotinic Effects

**Nicotine**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species, esp. dogs and other small companion animals</td>
<td>Minutes to 2 hours</td>
<td>Hours; often lethal</td>
</tr>
</tbody>
</table>

**Source**

- Alkaloid from *Nicotiana tabacum* (tobacco), 2 - 8% in leaves (dried).
- Nicotine sulfate.
  - 0.05 - 4.0% in dusts and sprays to control insects.
  - 40% in a concentrated solution (Black Leaf 40).
  - Also used in immobilizing agent (Cap-Chur-Sol) via projectile syringe (Cap-Chur Gun-dart); very narrow margin of safety.
- Cigarettes-up to 20 mg of nicotine each; cigars up to 40 mg. Cigarette butts contain about 25% of the total nicotine content.
- A pack of cigarettes was reported to be lethal to a dog.
- Snuff contains from 4.6 - 15 mg of nicotine/1 gram moist material.
- Chewing tobacco: 2.5 - 8.0 mg nicotine/1 gram dry material.
- Nicotine gum (Nicorette ®) contains 2.0 mg of nicotine. Its bioavailability is reportedly comparatively low at only 15%.

![Nicotine structure](image)

**Toxicity**

- LD₅₀ insects - 200 - 300 mg/kg.
- LD₅₀ oral mouse 24 mg/kg; oral rat 55 mg/kg.
- Minimum LD canine and feline: approx. 20 - 100 mg total dose.
- Lethal dose equine 100 - 300 mg total dose.
- Lethal dose ovine 100 - 200 mg total dose.
- A total dose in humans of 40 mg has been lethal.

**Absorption, Distribution, Metabolism and Excretion (ADME)**

- Poor absorption from the stomach. Absorbed from and also may cause some irritant effects on the mucous membranes of the mouth, pharynx, and esophagus. Alkalinization of the stomach enhances absorption.
- Potent emetic effect may limit intestinal absorption.
- Absorbed from the intestine, respiratory tract, intact skin.
- Nicotine from Nicorette® gum reported results in maximal blood concentrations of nicotine at 15 - 30 minutes after being chewed. The peak may be reached at a later time in dogs that may ingest it without chewing very much and that may also ingest wrappers that impede digestion.
- Undergoes metabolism in the liver, kidneys, and lungs.

**Mechanism of Action**

- Mimic of acetylcholine at sympathetic and parasympathetic ganglia, neuromuscular junctions of skeletal muscle and at some synapses in the CNS. Low doses cause depolarization and stimulation of receptors similar to acetylcholine. Higher doses cause stimulation followed by blockade at autonomic ganglia and myoneural junctions of skeletal muscle.
- Cardiovascular: stimulation of sympathetic ganglion and adrenal medulla leading to release of catecholamines.
- GI: parasympathetic stimulation leading to increased tone and motor activity.
- Death is a result of respiratory paralysis.

**Signs**

- Rapid onset (15 - 45 minutes after exposure) and progression of the syndrome (minutes to a few hours in most instances. Duration 1 - 2 hours following mild exposure to 24 hours following severe intoxication.
- Excitation, tachypnea, salivation, lacrimation, emesis, and diarrhea.
- Followed by: muscle weakness, twitching, depression, tachycardia, shallow, slow respiration, collapse, coma, cyanosis, cardiac arrest, death.

**Lesions**

Cyanosis, lesions possibly associated with an agonal death.

**Diagnosis**

- History of exposure to toxic amounts, signs and relative absence of lesions.
- Confirmation: Nicotine in urine, blood, liver, kidney or other tissues; or in gastrointestinal tract contents, vomitus, or lavage washings.

**Treatment**

- Poor prognosis with large doses.
- Sublethally dosed animals generally show some improvement within 3 hours or so.
- Dermal exposure-vigorously bathe with liquid dish detergent (or unmedicated shampoo: use thick rubber gloves to prevent human exposure; surgery gloves may not be an effective barrier to many different toxicants).
- Oral exposure: if thorough emesis has not occurred and if not contraindicated an emetic may be used. Alternatively, lavage or enterogastric lavage may be indicated.
- Activated charcoal should be left in the digestive tract. Repeated doses (up to 3) of a dilute slurry of activated charcoal may be of value at 2, 5, and 8 hours after the initial activated charcoal dose.
- Atropine may be used if parasympathetic effects are present-doses may be similar to those used for organophosphate toxicoses (work up to the dose however, starting with preanesthetic doses and repeating periodically until the appropriate response is achieved).
- Artificial respiration and oxygen as indicated. Fluid therapy if hypotension occurs.
- Nicotine toxicoses may be shortened by acidification of the urine which may promote urinary excretion. This must be reserved for animals which are not already acidotic as a result of respiratory impairment, cardiovascular dysfunction, exertion (tremors, etc.) or seizures.
- Control seizures if needed with diazepam or barbiturate.
- **Do not** administer antacids since nicotine is better absorbed from a more alkaline stomach.
Nicotiana spp. - Tobacco

N. tabacum - tobacco, burley tobacco
N. attenuata - coyote tobacco, wild tobacco
N. trigonella - desert tobacco
N. glauca - tree tobacco
N. trigonophylla

Family - Solanaceae.

Images

- Nicotiana spp. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Tobacco, burley tobacco, Nicotiana tabacum - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- Coyote tobacco, wild tobacco, Nicotiana attenuata - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- Tree tobacco, Nicotiana glauca - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.
- Desert tobacco, Nicotiana trigonophylla - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Habitat

- N. attenuata - Wyoming and Washington, to California and Mexico, especially S.W. USA, dry sandy soils, along dry stream beds.
- N. trigonella - Southern Nevada, Utah, and Colorado to California; Western Texas, Mexico and Central America, arid or semi-arid valleys.
- N. glauca - Southern USA, Texas to California, Along the Rio Grande, Mexico, Argentina, Hawaii, waste areas below 3000 ft.
- N. tabacum - USA, southeastern, and eastern states, cultivated fields.

Description

Rank, acrid herbs, annual or perennial, shrub or small tree, 1 - 4 feet tall. Sticky haired stem, with alternate leaves. Lower leaves are oblong to egg-shaped but upper leaves are more lanceolate with sharp or blunt tips. Leaves are simple and opposite, usually have smooth edges, broad, hairy, and sticky. Flowers are terminal or branched, 5-lobed, tubular and about 2 in. long, greenish-white, yellowish or lavender. Fruit is a 2 celled capsule with many seeds.

Toxic Principle

The alkaloids nicotine and teratogenic agents including anabasine, anatabine, and anabaseine. Carcinogenic polycyclic aromatic hydrocarbons such as benzo(a)pyrene are produced during combustion.

Absorption, Distribution, Metabolism and Excretion (ADME)

Nicotine in pesticides is rapidly absorbed from gastrointestinal tract and skin. Nicotine and other alkaloids, when present in tobacco,
may be absorbed more slowly.

Toxicity

- Tobacco plants are unpalatable and animals generally avoid consumption.
- The entire plant is poisonous, foliage contains a high content of nicotine; tops are most toxic.
- Because tobacco stalks are high in nitrogen, they are often returned to the soil to increase fertility and may poison foraging animals.
- Small animals ingest tobacco, which causes centrally mediated vomiting, therefore, tobacco poisoning is infrequently fatal.
- Horses have died as a result of eating leaves of harvested tobacco, when kept overnight in a tobacco barn. The minimum toxic dose is 0.68% of body weight.
- Children have been poisoned by sucking the flower; leaves used in salad have proven fatal.
- Fatalities are common in cattle. The minimum lethal dose of *N. trigonophylla* is approximately 2% of body weight on a green-weight basis.
- Estimated LD$_{50}$ in sheep 2.3 - 3.4 mg/kg of anabasine. *N. glauca* contains 0.45 - 1.14 mg of anabasine/gram of dry weight. Moderate to severe clinical signs occurred at levels that provided 0.56 - 0.78 mg anabasine/kg body weight. Gilts had moderate to severe signs when exposed at levels that provided 0.23 - 0.84 mg anabasine/kg body weight. At the upper dose levels, piglets were deformed at an incidence of about 50%.
- In sheep, the minimum toxic dose is 1.5% of the body weight and the lethal dose is 3.25% of BW.

Susceptible Species

- Cattle, swine, sheep, horses, and birds have been reportedly poisoned by ingestion of tobacco plants.
- Small animals (dogs, cats) have developed toxicosis following ingestion of tobacco containing products.

Mechanism of Action

- Initially stimulate ganglia of sympathetic and parasympathetic nervous systems by direct action on ganglion cholinergic receptors.
- Followed by ganglionic blockade due to persistent depolarization.
- CNS initially stimulated (tremors, convulsion) followed by depression.
- Death due to respiratory failure from neuromuscular blockade.

Signs

- Signs become apparent from 15 minutes up to several hours after exposure.
- Staring into space, wretching, vomiting, salivation, abdominal cramps, bloat, frequent urination, colic, diarrhea.
- Muscular weakness, staggering, tendency to fall on forelimbs, lameness, trembling, shivering, spasms, muscle tremors, 3rd eyelids drawn, blindness, dullness, stupor.
- Irregular, weak pulse, or violent palpitation of the heart.
- Prostration, opisthotonus, diaphragmatic spasms.
- Elevated body temperature, but extremities feel cold.
- Dyspnea, respiratory paralysis and death.
- In swine, the primary problem is teratogenesis. Pregnant sows eating tobacco stalks may give birth to pigs with arthrogryposis. Arthrogryposis is a flexion, anterior or posterior of limbs with medial deviation of limbs. Day 35 seems to be the end of the dangerous period. As an apparent result of the limb deformity, prolongation of parturition kills many pigs from neonatal asphyxiation. Sows may not show signs of toxicosis before giving birth to malformed pigs.
- Sometimes over 1/2 the pigs on a farm are born abnormal. Unable to nurse normally, piglets may die from hypoglycemia.
  - No effect on fertility of sows.
  - No increase in abortions.
- Teratogenic effects noted in offspring from sheep feeding on *N. glauca* during the 30 - 60th day of gestation. Teratogenic effects included carpal flexure, lordosis, facial deformities, and cleft palate.

Lesions

- There may be ingesta in the trachea or lungs from aspiration. In ruminants, the abomasum may be congested, and there may be engorgement of subcutaneous blood vessels. Obviously, these lesions are non-specific.
- Arthrogryposis: Affects primarily the appendicular skeleton, but the spinal column and mandible have been affected. There may also be clubbing of one or more feet and acute kyphosis (humpback) and brachygnathia. Affected bones become thickened, curved, twisted, or shortened, and there may be malalignment of joints.
**Treatment**

- Emetic if no contraindications exist.
- Lavage followed by administration of activated charcoal and saline cathartic.
- Artificial respiration and oxygen therapy may be required.

**Prevention**

Supplemental feed, when forage is scarce will reduce the likelihood of toxicosis. Pregnant swine should not be pastured on tobacco stalks/roots.

**Tree and Desert Tobaccos** - The large oval leaves of tree tobacco are shown above, the flowers in the center, and the seed (enlarged) in the right center. The flowers, leaves, seed (enlarged), and seed pods of desert tobacco are at lower left.
Lobelia

Lobelia inflata - Indian tobacco, lobelia, eye bright, asthma weed, gag root, puke weed, wild tobacco
L. siphilitica - Great blue lobelia, great lobelia, high belia, Louisiana belia, Blue cardinal flower
L. dortmanna - Water lobelia
L. cardinalis - Cardinal flower, hog physic, Indian pink, red lobelia, scarlet lobelia
L. berlandieri - Berlandier lobelia

### Images

- Lobelia spp. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.

### Habitat

- *L. inflata.*
  - Eastern Canada to Georgia; less common in areas westward to Nebraska and Arkansas. Meadows, pastures and cultivated fields.
- *L. siphilitica.*
  - Eastern USA and north central states. Near springs and swampy ground or wet pastures.
- *L. dortmanna.*
  - Northern USA, Canada and Europe. In shallow water or immersed borders of ponds, lakes and streams.
- *L. cardinalis.*
  - Quebec to Minnesota, southward to the southeast corner of Colorado, and east to Texas and Florida (includes Midwest).
- *L. berlandieri.*
  - Texas gulf coast (Hidalgo, Cameron, and Willacy counties) in moist habitats; Mexico.

### Description

- *L. inflata*
  - Erect, 12 - 32 inches tall, with milky sap. The stem is densely branched, and hairy. Leaves are alternate, ovate to oblong, toothed. Flowers are in loose racemes, tubular, 5 lobed, with 5 stamens, and pale blue in color. The fruit is 2 celled, opens at the apex and contains many seeds.
- *L. siphilitica.*
  - Erect (3.3 feet tall) perennial, somewhat hairy stem that is stout and mostly simple. Leaves are alternate and ovate to
lanceolate, thin and pointed at both ends, 2 - 6 inches long and irregularly serrated. Flowers are leafy, 3/4 inches long and bright blue to rarely white.

- *L. dortmanna*.
  - Very smooth perennial, with a simple stem. Leaves are clustered at the base, linear and hollow. Few flowers are present in loose racemes, white or pale blue.
- *L. berlandieri*.
  - Annual with erect or decumbent stems that are smooth and glabrous or sparsely hairy near the base. Stems usually bear 12 or fewer leaves which become papery when dry. Lower leaves often crowded into a rosette at the base of the plant leaves.

**Toxic Principle**

- Alkaloids lobeline and lobelidine. Altogether there are at least 14 pyridine alkaloids which are similar to nicotine.
- Lobeline stimulates carotid body chemoreceptor, interacts with nicotinic acetylcholine receptors, and is a respiratory stimulant.
- *L. berlandieri* may contain N-methyl piperidine.

**Toxicity**

- Entire plant is toxic. Dermatitis may result in man from contact with the leaves. Overdoses from home medicines made from this plant (dried leaves, tops) have proven fatal. Toxic quantities are not commonly ingested.
- Roots and seed capsule considered most toxic. Alkaloid content of plant varies from 0.13 - 0.63%. Highest alkaloid concentrations just before and after plant flowers. Flower stalks can have 0.9 - 1.1% lobeline.

**Susceptible Species**

- Include sheep, cattle and goats (and probably all other warm-blooded species). Signs include sluggishness, salivation, diarrhea, anorexia, and nasal secretion. Hemorrhage, ulceration about the mouth and coma. Dilation of pupils.
- *L. berlandieri* (in cattle and goats).
- Apparent outbreaks of *L. berlandieri* toxicosis have affected up to 1500 cattle and 500 goats.

**Signs**

- Lobeline (general).
  - In humans: nausea, vomiting, perspiration, exhaustion, weakness, prostration, mydriasis, pain, paralysis, depressed body temperature, rapid feeble pulse, stupor, tremors, coma, convulsions, and death.
- *L. berlandieri* in cattle: causes profuse salivation, dilation of pupils, atrophy of leg muscles, and extreme narcosis but animals retain normal appetites.

**Lesions (All Species of Lobelia)**

- Nonspecific. Widely distributed hemorrhage may be seen but mild gastroenteritis is more likely to be observed.
- *L. berlandieri* subcutaneous hemorrhage, subdural edema, and congestion of brain.

**Treatment**

If not contraindicated, induce emesis. Otherwise consider lavage, activated charcoal, saline cathartic. Provide respiratory support if needed. Treat any seizures with diazepam.
Cardinal Flower - Distinctive red 2-lipped tubular flowers and lance-shaped leaves are characteristic of this tall colorful herb. At right center the enlarged seed capsule and pitted seed are shown.
Lobelia inflata and Lobelia siphilitica.
**Lobelia inflata**, Indian tobacco. - A, plant showing general habit; x 1/3. B, flower; x 2. C, seed; x 18. **Lobelia dortmanna**. Water lobelia. E, plant; x 1/3. F, flower; x 1/2. G, capsule; x 1/3. **Lobelia siphilitica**. Great lobelia. H, flowering shoot; x 1/3. I, flower; x 1/2.

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**Conium - Poison Hemlock**

*Conium maculatum* - Poison hemlock, European hemlock, spotted hemlock

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, swine, poultry, horses, sheep</td>
<td>Minutes to hours</td>
<td>Hours; potentially lethal; teratogenic</td>
<td></td>
</tr>
</tbody>
</table>

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**Images**

Description

- Coarse, erect, biennial herb, 1 - 3 m tall.
- Smooth, purple spotted, hollow stems. Purple spots more prominent near base.
- Parsley-like alternate, compoundly dissected leaves.
- Flowers are small, white, and in umbrella-shaped clusters. Terminal umbels of flowers 4 - 6 cm across.
- Leaves smell like parsley when crushed. Crushed stems, leaves, and roots may have pungent odor.
- Nauseating taste.

Habitat

- Fertile soils and fields, fencerows, roadsides, meadows, along streams.
- Native in Europe but now in most of USA, common in midwest among other areas.

Toxic Principles

- Piperidine (nicotinic) alkaloids including \( \gamma \) coniceine, coniine, N-methyl coniine, conhydrine, and pseudoconhydrine.

- Alkaloid content variable with stage of development and stage of reproduction of plant.
- First year plant low alkaloid content. Plants in second year have alkaloid contents of approximately 1% in all plant parts.
- Alkaloid content is somewhat higher after sunny weather, as compared to rainy weather.
- Vegetative stage-Early, primarily \( \gamma \) coniceine.
- Coniine (2-propylpiperidine) and N-methyl coniine progressively increase in flowers and fruits while \( \gamma \) coniceine decreases during plant development.
- Highest concentration of alkaloids is in seeds which can contaminate poultry and swine cereal grains.
- \( \gamma \) coniceine and coniine are the primary teratogenic alkaloids of *Conium*.

Toxicity

- Tea made from poison hemlock reportedly killed Socrates.
- Cows displayed severe clinical signs at 3.3 mg coniine/kg bw.
- Mares have severe signs at 15.5 mg/kg and ewes appeared most resistant requiring 44.0 mg/kg of coniine before severe clinical signs developed. At these levels no teratogenic effects were noted in offspring from pregnant mares or ewes.
- Fatal poisoning in swine with 9 g/kg bw of fresh immature plant.
- Similar range of toxicity seen with parenterally administered alkaloid extracts.

Susceptible Species

- Spontaneous (natural) exposure has caused poisoning in cattle, swine, elk, and poultry.
- Toxicosis experimentally reproduced in sheep and horses as well.
Poisoning

Eaten mostly in early growing season.

Mechanism of Action

- Coniine stimulates and then depresses autonomic ganglia and motor end plates in skeletal muscle.
- Large doses can cause neuromuscular block.
- Effects are similar to nicotine but have greater CNS and neuromuscular paralytic effects.

Signs

- Systemic effects.
  - Initially nictitating membranes of eyes closed, producing temporary (15 - 30 minutes) blindness in affected sows. Mydriasis.
  - Muscle tremors, ataxia, muscle weakness. "Nervousness" first followed by severe depression.
  - Frequent urination, defecation.
  - Hypersalivation.
  - Abdominal pain.
  - Incoordination, recumbency.
  - Breathing ceases before cardiac arrest. Death due to respiratory paralysis.
- Teratogenic effects. Deformities in joints are prominent.
  - Occur in (at least) calves and piglets and may include:
    - Crooked legs (crooked calf disease, arthrogryposis).
    - Cleft palate.
    - Kinked tails.
  - Arthrogrypotic skeletal malformations occur in calves when poison hemlock is ingested by pregnant cows between days 40 through 70 of gestation. Similar skeletal lesions occur in swine between days 42 through 61 of gestation.
  - Cleft palates can be induced in piglets if pregnant gilts ingest poison hemlock between days 30 through 45 of gestation.

Diagnosis

- Appropriate exposural history and clinical signs.
- "Mousy" odor to urine and expired air.
- Differential diagnosis for teratogenic effects include lupine species, *Nicotiana* sp., and poison hemlock.

Treatment

- Rapid onset-fairly rapid recovery.
- Activated charcoal, appropriate steps to evacuate the GI tract.
- Saline cathartic.
- Support respiration.
- Atropine may be given if severe parasympathetic signs are present (cautious in horse: avoid stasis of the gut!). If gastrointestinal effects not severe, it may be best to avoid atropine in any species because of atropine-induced delayed intestinal transit which may increase absorption.
- Gastric or rumen lavage or rumenotomy may be of benefit if recently ingested. However, the stress involved may exacerbate clinical signs of the toxicosis.
Poison-Hemlock - Note the large pinnately divided leaves, the flat-topped clusters of flowers and fruits, the female flower (enlarged, lower right) with enlarged male flower above, and ribbed fruit capsule (enlarged, right center) of this poisonous herb.

Lupinus - Lupine or Bluebonnet
Lupinus leucophyllus - Velvet lupine, wooly-leaved lupine
Lupinus leucopsis - Big bend lupine (may be the same plant as L. sericens listed below)
Lupinus argenteus - Silvery lupine
Lupinus sericens - Silky lupine
Lupinus cyanus
Lupinus onustus - Plumas lupine
Lupinus laxiflorus - Douglas spurred lupine, loose flower lupine
Lupinus alpestris
Lupinus caudatus - Kellogg's spurred lupine
Lupinus greenei
Lupinus pusillus - Low lupine
Lupinus polyphyllus - Washington lupine

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<td>Sheep, cattle, and other herbivores</td>
<td>1 - 24 hours</td>
<td>Hours to days; potentially lethal; teratogenic</td>
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Images

Several other species also may be toxic including garden lupines planted in the midwest and east which may be responsible for rare toxicoses in children or small animals.

Habitat

- Approximately 100 species of lupine are present in the USA and Canada. Most are present in states and provinces from the Rocky Mountains westward.

Description

- Range species are mostly low, perennial shrubs; with alternate leaves which are palmately compound; with 5 - 17 leaflets, most leaflets are oblanceolate. Some *Lupinus* spp. are annuals.
- Flowers are terminal, often showy, blue, white, red or yellow with 10 stamens, and filaments are united in a single tubular structure; anthers are free, and alternating long and short.
- Fruit is a several-seeded, flattened legume pod.
- Begin to grow in early spring, flower in June, and form pods and seeds in late summer (July-August).

Toxic Principle

- More than a dozen quinolizidine alkaloids, but some piperidine alkaloids and other types of alkaloids have also been isolated from species of *Lupinus*. These alkaloids are largely nicotinic in effect. The nitrogen oxides of some of these bases have also been detected in some lupines.
- The alkaloids are present in the foliage but the greatest concentration is in the seeds.
- Anagyrine is a teratogenic alkaloid in *L. caudatus* that reportedly affects cattle but not sheep.

Conditions of Poisonings

- Cause more deaths than any other single plant in Montana, Idaho and Utah.
- Species and taxonomic differentiations between species are insufficiently characterized.
- Different lupines produce varying syndromes in a given species of livestock. Seasonal variation in toxicity in a given species of lupine exist and many species are acceptable forage under range conditions.
- Plants which are in the preflowering stage of maturity are unlikely to be hazardous, under normal range circumstances, except in the case of *L. leucophyllus* which may cause toxicosis as a result of consumption of young plants. Alkaloids are not lost upon drying. Range hay may be highly toxic if the seeds are retained; this occurs when the majority of the pods are immature; mature pods open when drying and the seeds are dropped as the hay is handled. For many lupines, the time and degree of seeding varies from year to year.
- Most losses occur under conditions in which animals consume large amounts of pods in a brief period, such as when they are being
driven through an area of heavy lupine growth, unloading animals into such an area, trailing animals through an area where the grass is covered by snow but the lupine is not or when feeding podded lupine hay, which is apparently palatable.

- Most serious poisoning, therefore occur in the fall; lupine remains green after other forage has dried.

**Toxicity**

- Seeds alone are toxic to sheep at 0.25 - 1.5% of their body weight.
- Adverse effects in sheep occur when ingested 60 - 125 grams of lupine daily for 3 - 4 days.
- 0.5 - 0.75 kg of lupine can induce adverse effects in cattle.
- *L. laxiflorus* is more toxic to cattle, less toxic to sheep.

**Susceptible Species**

- Several outbreaks involving the loss of over 1000 sheep are on record.
- If other forage is available, sheep, the most commonly affected species, will avoid lupine.
- Goats, swine and deer have also been poisoned.
- Poisoning is rare in cattle and horses, because they usually do not readily consume the pods.

**Signs**

- Characteristic labored breathing (snoring) in sheep, with depression, salivation, ataxia, clonic spasms, head pressing tremors, seizures and coma, and frequently death. Death may be preceded only by coma and no other signs (no struggling) or alternatively, preceded by violent attacks on other animals or objects.
- Signs may appear as early as one hour after ingestion or as late as 24 hours after consumption. Death may occur within one day or occur several days later and is a result of respiratory paralysis.
- Cattle under range conditions rarely display clinical signs.

**Teratogenesis**

- Lupine ingestion is one cause of crooked calf disease which occurs in South Dakota, Nebraska and west to the Pacific, north to Canada. Incidence of crooked calves is highly variable geographically and from year to year within a given herd. Three to 35% of a given calf crop may be affected. Affected, malformed calves are usually born alive at full term and lesions include misaligned joints and twisted bones (arthrogryposis). In mild cases, deformity is confined to a mild bowing of the forelegs. In severe case, the forelegs are twisted and held in a flexed position.
- The neck and back may also be involved and rarely the rear legs.
- A cleft palate is sometimes present.
- No particular breed predilection or genetic pattern has been found.
- Under some circumstances, it is always associated with early calves and may ther efore be controlled by delayed breeding. The dangerous period of exposure during pregnancy is during days 40 - 70 of gestation. Slight to moderate deformities can occur from ingestion of lupines before and after this stage of gestation (30 - 100 days).
- The crooked calf syndrome has been reproduced by the experimental feeding of the alkaloid, anagyrine (at 30 mg/kg), the most teratogenic alkaloid of lupine.

**Note**

- European lupines differ in that they may also be hepatotoxic.
- Lupinosis of Australia is related to a hepatotoxic and is another entity, not to be confused with lupine poisoning in the USA.
**Lupine (Lupinus sericeus)** - All the species of Lupine are supposed to be poisonous, and are the cause of the larger part of the heavy losses of sheep during the late summer and fall months. Sheep are most likely to be poisoned by eating the pods and seeds.

**Few-Flowered Lupine (Lupinus sparsiflorus)** - Note the digitately divided leaves, the hairy foliage, the pea-shaped flower (lower left), and the flattened hairy seed pod and seed (enlarged, lower right) of this unusual plant.
**Sophora - Mescal Beans**

*Sophora secundiflora* - Mescal bean, burn bean, carol bean, red bean, and frijolillo. Sometimes called Texas mountain laurel (do not confuse with *Kalmia*, a more well-known mountain laurel)

*Sophora nuttalliana (formerly Sophora sericea)* - Silky sophora

*Sophora stenophylla*

*Sophora tomentosa* - Necklacepod sophora, silver bush

*Sophora japonica*

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(See Toxicants with Mixed Effects on the Central Nervous System)

**Family** - Leguminosae (Pulse or Bean Family)

**Images**


- Silky sophora, *Sophora nuttalliana* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

- *Sophora stenophylla* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.


- *Sophora japonica* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

**Description**

- *S. secundiflora*.
  
  - Woody evergreen shrub or small tree (3 - 10 meters tall) in the pea family. Leaves are alternate, pinnately divided into 5 - 13 oblong leaflets. Leaflets have silky hairs on the underside and a shiny yellow-green surface above. Pea-like flowers are violet-blue, fragrant and grow in dense terminal clusters up to 4 inches (10 cm) long. One to 8 seeds are bright red and 1/2 inch (1.25 cm) in diameter in a woody pod, 1 - 7 inches long, just over 1/2 inch (1.25 cm) in diameter.

- *S. nuttalliana*.
  
  - Plant is erect, 4 - 12 inches (10 - 30 cm) high. Stem is silky, woody at base. Leaves are alternate, pinnately compound; 7 - 25 hairy, oblong leaflets 0.5 - 5.0 inches (1.25 - 13 cm) long. Flowers are white. Fruit is a few-seeded, hairy, leathery pod 0.8 - 2.0 inches (2 - 5 cm) long.

- *S. tomentosa*.
  
  - Shrub, numerous branches with compound leaves. Flowers grow in raceme and are bright yellow. Pea-like yellow seeds contained in pods.

**Habitat**

- Limestone hills, rock ledges, and canyons.

- *S. secundiflora*.
  
  - Plants are native to southwestern Texas, southern New Mexico, and northern Mexico, and cultivated as showy ornamentals elsewhere in the Southwest. Plants grow best on limestone soils: range, hills, canyons.

- *S. nuttalliana*.
  
  - Nebraska and Kansas to Texas and Arizona: prairies and Great Plains.

- *S. tomentosa*. 
Additional Sources

- The seeds (mescal beans) were once used in medicine as a narcotic and hallucinogenic drug by Indians of Mexico and the Southwest. The drug produces intoxication characterized by excitement and delirium followed by deep sleep lasting a few days. Its use is no longer common (1990s).
- Mescal beans have been used extensively to make necklaces. Chewing the necklace beans can cause poisoning.

Toxic Principles

- The entire plant, especially the seed, is poisonous. These plants contain quinolizidine alkaloids.
  - *S. japonica*.
    - Contains the nicotinic cytisine, the cardiotoxic and myotoxic lupanine, and the cardiotoxic and potential neurodepressant matrine, as well as lectins similar to compounds produced in the bark of black locust (*Robinia pseudoacacia*).
  - *Sophora* is not the source of the hallucinogenic drug mescaline, which comes from the "mescal buttons" of peyote (*Lophophora williamsii*), and which also is produced synthetically.

Toxicity

- The LD$_{50}$ for seed pods of some *Sophora* spp. in large animals is reported to be 0.5 g/kg. Toxin(s) may be somewhat cumulative.
- One thoroughly chewed seed is sufficient to cause the death of a child, but the hard unbroken whole seeds may pass through the digestive tract without harm. Mature foliage is more toxic to livestock than immature and may be harmful to humans if eaten or used to make tea.
- Several other southwestern species of *Sophora* also contain toxic alkaloids but are apparently less toxic than mescal bean.
- Suspected teratogen. In a pilot study by Keeler, *S. stenophylla* was teratogenic.

Susceptible Species

- Cattle, sheep, goats, and man. Poisonings in small animals possible. Cattle may be most often poisoned.

Signs (*S. secundiflora*)

- Mucous membrane irritation, salivation.
- Nervousness, violent tremors, exercise-induced rigidity of rear legs, tremors, especially over shoulders and rump.
- Nausea, vomiting, diarrhea, excitement, delirium, hallucinations, paralysis, coma, and death due to respiratory paralysis. Nonlethal doses may cause a deep sleep that lasts for 2 - 3 days.
- Sheep usually recover after a time; cattle often die: cattle are more susceptible than sheep or goats.

Lesions

- None reported apart from teratogenic effects.
- Teratogenesis (arthrogryposis or contacted tendons) is believed to be associated with some species of *Sophora*.

Treatment

- Activated charcoal and cathartic.
- Treat as for nicotine toxicosis. Seizure control, correct hypotension (i.e., fluids), atropine for parasympathetic signs, e.g., bradycardia.

Prevention

- Supplemental feeding when other forage is scarce.

Note

Don't confuse *S. secundiflora* (Texas mountain laurel) with *Kalmia* spp., the much more commonly encountered (in appropriate areas of the country) plant known as mountain laurel, which causes an entirely unrelated (andromedotoxin-mediated) syndrome.
**Sophora secundiflora (mescal bean)** - The plant has pinnately divided leaves, clusters of purplish pea-like flowers (enlarged, left center), constricted pods (lower center), and bright red seeds (enlarged, lower left).

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**Gymnocladus dioica - Kentucky Coffee Tree**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep, cattle, horses</td>
<td>1 to a few hours</td>
<td>Hours to days; potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Synonyms** - American coffee berry, Kentucky mahogany, nicker tree, stump tree

**Family** - Leguminosae, the bean family

**Images**

- Kentucky Coffee Tree, *Gymnocladus dioica* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Habitat**


**Description**

- A large tree (60 - 100 feet tall), with rough bark and many major branches. Leaves are bipinnately compound, and the leaflets are stalked, with large ovate shape, feather-like.
- Seven to 13 leaflets per stalk.
- Flowers are greenish-white, small and fragrant, in racemes. Fruits are comprised to pods, brown to maroon, hard, flat and 6 - 10 inches (15 - 25 cm) long and 1 - 1.5 inches (2.5 - 4 cm) wide.
- Seeds (4 - 7) are hard, somewhat flattened, oval, and broad, and 1.5 inches (4 cm) in length.
Toxic Principle

Uncertain, possibly the quinolizidine alkaloid, cytisine, which acts like nicotine.

Toxicity

Sprouts eaten in the spring have produced toxicosis. Pods and seeds on the ground eaten in the fall or winter have produced poisoning. Leaves, young sprouts and seeds with the gelatinous material around them contain the toxin. Sheep, cattle, horses and humans have been poisoned.

Signs

- Generally rapid (< 1 hour) onset of clinical signs.
- Intense gastrointestinal irritation, profuse diarrhea and straining, vomiting, hypertension, bradycardia, respiratory depression, muscle paralysis, and convulsions.
- Animals often display depression.
- Death within a day after clinical signs appear.

Lesions

Gastroenteritis, congestion of mucous membranes.

Comments

Humans have been poisoned by using the seeds as a coffee substitute.

Treatment

- Nonspecific, activated charcoal, saline cathartic, supportive and symptomatic.
- Evacuate gastrointestinal tract as condition permits.
- Atropine for parasympathetic signs, e.g., bradycardia.
- Artificial respiration is usually impractical (LA primarily affected), therefore it is important to avoid absorption of highly toxic amounts.
- Treat seizures if develop with diazepam, phenobarbital, pentobarbital, or chloral hydrate in large animal.
- To correct hypotension, fluid therapy may be required.
Kentucky Coffee Tree, *Gymnocladus dioicus* (L.) K. Koch.

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**Laburnum anagyroides - Golden Chain**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Affect the Autonomic Nervous System (and, in some Cases, Voluntary Nerves as Well)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbivores</td>
<td>Within a few hours</td>
<td>Hours to 2 days; potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Synonyms** - Bean tree, laburnum

**Family** - Leguminosae

**Images**

- Golden Chain, *Laburnum anagyroides*. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org . -
- Golden Chain, *Laburnum anagyroides* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
Habitat

Most of the USA and Great Britain. Planted as an ornamental for its hanging racemes.

Description

Large ornamental shrubs or small trees, up to 20 - 30 feet tall, deciduous. Trifoliate, long petioled leaves, alternate with 3 clover-like leaflets, which are downy beneath. Flowers-hanging racemes, 1 1/2 feet long, golden yellow flowers, shaped like sweet peas, 3/4 inch across. Blooms until late spring. Fruit is a legume pod, containing up to 8 seeds, flat, 2 inches long. Root has a licorice taste.

Toxic Principle

The quinolizidine alkaloid, cytisine.

Toxicity

Considered to be the second most toxic tree in Britain. Action is similar to nicotine. Oral toxic dose of seeds in horse is 0.05% of the animal's weight. Cytisine is excreted in the milk. Roots have proven fatal to cattle. Young pods and seeds are highly toxic. Humans also poisoned.

Signs

- Excitement, incoordination, convulsions, coma and death due to asphyxiation.
- Additional signs include nausea, vomiting, diarrhea, and mydriasis.

Treatment

Same as for nicotine toxicosis.

Prevention

The likelihood of toxicosis can be reduced by removal of the flowering portion shortly after blooming.
Golden Chain (laburnum)
Levamisole

Introduction

Levamisole is 1-2,3,5,6-tetrahydro-6-phenyl-imidazo [2,1-b]-thiazole hydrochloride. It is a white crystalline powder that is highly water soluble.

Uses

Anthelmintic, microfilaricide, immunostimulant.

Mechanism of Action

Depolarization of nerve cell membranes. Proposed to act as a nicotinic-like ganglionic stimulant. It may have both nicotinic and muscarinic effects at cholinergic receptors. First there is stimulation, then blockade of the ganglionic and skeletal muscle transmission.

Toxicity

- Sheep (oral):
  - 5 times therapeutic dose-signs begin.
  - Therapeutic dose = 8 mg/kg.
  - Oral lethal dose = 90 mg/kg.
- Swine:
  - > 5 times therapeutic dose in feed or > 3 times therapeutic dose in water-signs begin.
  - > 4 - 8 times therapeutic dose with SQ route-signs begin.
  - Therapeutic dose = 8 mg/kg.
  - SQ lethal dose = 40 mg/kg.
- Cattle:
  - > 3 times therapeutic dose-signs begin.
  - > 2 times therapeutic dose with SQ route-signs begin.
  - Therapeutic dose = 8 mg/kg.
- Dogs:
  - ≥ 4 times therapeutic dose-signs begin.
  - Therapeutic dose = 10 - 11 mg/kg.
- Horses:
  - ≥ 2 times therapeutic dose - signs begin.
  - Therapeutic dose = 7.5 - 15 mg/kg.
- The metabolites are less toxic than the parent compound.

Contraindications
Nicotine and nicotine-like agents may enhance the toxicity of levamisole thus decreasing the LD50. Not approved for use in lactating dairy cattle. No adverse effects have been reported with concurrent use of topical diazinon or malathion.

Clinical Signs

- Cattle, sheep, goats, swine, and horses:
  - Hypersalivation (may have muzzle foaming in cattle at normal dose for a few hours), head shaking, lip licking, vomiting in swine, muscle tremors, ataxia, anxiety, hyperesthesia, irritability, clonic convulsions, CNS depression, rapid respiration, dyspnea, frequent urination, frequent defecation, collapse, prostration.
  - Death usually due to respiratory failure.
- In sheep and goats, the onset of signs occurs within 15 minutes, effects peak by about 30 minutes, and recovery occurs within 1 - 6 hours.
- In swine, a subcutaneous overdose may lead to dyspnea and death within 5 - 60 minutes.
- Dogs:
  - Vomiting, hypersalivation, depression, diarrhea, anorexia, cardiac arrhythmias, dyspnea, behavioral changes, pulmonary edema, tachypnea, ataxia, muscle tremors, seizures, death due to respiratory failure.
  - Hemolytic anemia has occurred in some dogs due to repeated dosing.
  - Also, this may cause an increase in alkaline phosphatase due to a change in osteogenesis.

Lesions

Congestion of the splenic red pulp, neutrophilic infiltrates in the lung parenchyma, marked subepicardial hemorrhage, intense enteritis, acute hepatic degeneration with marked subcapsular hemorrhage, massive hepatic necrosis, thalamic hemorrhage.

Residues

- The fat, muscle, and blood are free of detectible residues within 24 hours after ingestion of feed or water.
- The liver is free of residues within 72 hours.
- Label recommendations should be followed for proper use and withdrawal times.

Diagnosis

This is made primarily by a history of an overdose being administered, onset, and manifestations of clinical signs.

Treatment

Decontamination-emesis is recommended if possible within 1 hour of ingestion. After vomiting has subsided, activated charcoal and a saline cathartic are recommended. Careful monitoring of the patient is critical. Symptomatic and supportive therapy is of value if signs of significant intensity develop. This may include fluids, oxygen, and artificial respiration as indicated. Atropine has been suggested as an antagonist, but it does not decrease mortality. If needed, control seizures with diazepam or a barbiturate.

Imidacloprid

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small animals?</td>
<td>Minutes to hours</td>
<td>Unlikely to be lethal</td>
</tr>
</tbody>
</table>

Advantage®, Premise®, and Merit®. More potent agonist at nicotinic receptors of arthropods than those of mammals.
5. Nicotinic antagonists

**Succinylcholine and nicotinic antagonists**

<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>Succinylcholine</td>
<td>All species</td>
<td>Minutes</td>
<td>Minutes; potentially lethal</td>
</tr>
</tbody>
</table>

Succinylcholine is a nicotinic antagonist used during surgery to block neuromuscular junction receptors and produce paralysis and thus muscle inactivity. It is structurally similar to acetylcholine.

**References**

**Introduction to Anticholinergic Agents**


**Henbane (Hyoscyamus Niger)**


**Datura Stramonium - Jimson Weed**


**Introduction to Solanaceae, Solanine, Solanidine, Solanocapsine, as well as Atropine and Atropine-like Toxins in the Solanaceae**


**Cestrum spp. - Jessamines**


**Solanum spp. - Nightshade Group**


**Slaframine**

Organophosphorus and Carbamate Insecticides


Anabaena Flos-Aquae - Blue-green Algae

3. Mahmood NA, Carmichael WW. Anatoxin-a(s), an anticholinesterase from the cyanobacterium Anabaena flos-aquae NRC-525-17. Toxicon 1987; 25:1221-1227.

Nicotine


Nicotiana spp. - Tobacco


Lobelia


Conium - Poison Hemlock

**Lupinus - Lupine or Bluebonnet**


**Sophora - Mescal Beans**


**Laburnum Anagroides - Golden Chain**


**Levamisole**


**Imidacloprid**


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