In: *Veterinary Toxicology*, V. Beasley (Ed.)
Publisher: International Veterinary Information Service (www.ivis.org), Ithaca, New York, USA.

**Toxicants that Primarily Cause Respiratory Paralysis** (9-Aug-1999)

V. Beasley

Department of Veterinary Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA.

**Chapter Sections**

**Hydrogen Sulfide (H₂S)**
**Aminoglycoside Antibiotics and Skeletal Muscle Relaxants**

---

**Hydrogen Sulfide (H₂S)**

<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 Primarily Cause Respiratory Paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swine, all species</td>
<td>Minutes to 2 hours</td>
<td>Few hours, generally animals in confinement are affected; rapid death occurs; major hazard to farm workers</td>
<td></td>
</tr>
</tbody>
</table>

**Characteristics**

- Colorless.
- Heavier than air (sp. gr. 1.189).
- Flammable and explosive.
- Characteristic odor of rotten eggs.
- Produced by anaerobic bacteria during the decomposition of protein and other sulfur containing organic matter.

**Source**

- Liquid manure holding pits.
- Continuously produced and retained within the pit (solubilized in the liquid contents rather than free as a gas).
- The concentration of H₂S found in most closed animal facilities is generally in the area of 10 ppm, a nontoxic concentration.
- Agitation of the waste slurry, for example: resuspending solids prior to pumping the contents out or restarting units which were intended to continuously circulate water through the pit and have failed, will cause the sudden release of hydrogen sulfide producing concentrations of 100 ppm or greater.
- Another source of hydrogen sulfide is in deposits of natural gas, crude oil and some coal deposits. Sour gas (oil wells) is a mixture of aliphatic and aromatic hydrocarbons, hydrogen sulfide, and other volatile sulfur-containing compounds. Hydrogen sulfide is considered the most toxic constituent.
- Other industrial sources include hydrogen sulfide as a by-product, waste material, and H₂S leaks during its use or storage as a reactant in chemical synthesis.
- Other sources of sulfur, even oxidized forms such as sulfate in water or gypsum are thought by some workers to be reduced in the rumen to form H₂S and thus to induce chronic hydrogen sulfide toxicosis.
Toxicity and Clinical Signs

- Humans can detect low concentration such as 0.025 ppm which are nontoxic.
- Concentrations greater than 200 ppm hydrogen sulfide paralyze the olfactory apparatus eliminating the normal avoidance responses of exposed humans.
- At concentrations of above 300 ppm, the gas is a potentially imminent threat to life.
- Between 500 and 1000 ppm the effects of hydrogen sulfide may include permanent damage to the nervous system. Apnea can occur.
- At 1500 ppm, the course of events is the same, except the reaction is more intense.
- At greater than 2000 ppm, breathing becomes paralyzed after a breath or two, due to a direct paralyzing effect on the respiratory center. Generalized convulsions frequently occur at this time. Breathing is not reestablished in unassisted patients although temporarily the heart will continue to beat until the asphyxia results in death.
- In the presence of artificial respiration, or in the less severely affected animal which has not yet become apneic, the gas can be effectively eliminated from the body if sufficient exchange with uncontaminated air takes place.
- Ocular and respiratory tract irritation can occur. Threshold for serious eye injury is 50 - 100 ppm.
- Animals may exhibit brief excitement followed by listlessness decreased responsiveness to stimuli and inability to rise.
- Sometimes animals show mental derangement ("crazy behavior") and irritability.
- Secondary pulmonary and/or ocular bacterial infections may occur in affected surviving animals.
- Chronic long-term effects in humans include neurological, pulmonary, cardiovascular, and ocular disabilities.

Mechanisms of Action and Clinical Signs

- Sulfide ions act as direct cytotoxins, bind to cytochrome oxidase within mitochondria, and block electron transport. Syndrome differs from cyanide (another cytochrome oxidase inhibitor).
- Hydrogen sulfide is an irritant gas causing local inflammation of the moist mucous membranes of the eye and respiratory tract. The entire respiratory tract is irritated, but the deeper structures of the lung are irritated the most. This can result in pulmonary edema.
- Although the heart and skeletal muscles may be affected, the primary effect is on the chemoreceptors of the carotid body, which are stimulated leading to rapid breathing and secondary depletion of carbon dioxide (hypocapnia) from the blood. This in turn results in a period of respiratory inactivity (apnea). If depletion of CO2 does not proceed too far, the subsequent accumulation of carbon dioxide may again stimulate respiratory exchange. If however, spontaneous recovery does not occur and artificial respiration is not immediately provided, death from asphyxia is the inevitable result.

Lesions

Animals dying as a result of hydrogen sulfide toxicosis are generally cyanotic and may exhibit pulmonary irritation and possibly pulmonary edema.

Prevention

- Manure pits should not be agitated without removing the animals from the enclosed area. If this cannot be done, maximum air exchange should be present in the form of widely opening the building and using the full power of fans present, regardless of the time of the year. When mechanical fans are not present, procedures which may increase hydrogen sulfide release from animal wastes should not be performed until a stiff breeze will provide adequate exchange of air.
- Persons should not enter building with suspected hydrogen sulfide contamination due to the imminent hazard present to human health. Pumps should be turned off and the building thoroughly ventilated until the gases have had time to escape. Manure pits and septic tanks should not be entered, even when empty.
Treatment

- Remove from source of gas. **Must consider human risks involved.** Provide good ventilation.
- Cardiopulmonary support and resuscitation. Hyperbaric oxygen therapy has been advocated in affected humans.
- Treatment for pulmonary edema if present.
- Nitrite administration and subsequent methemoglobinemia production (as per cyanide toxicosis) has been advocated for treatment. The goal is to result in sulfmethemoglobin which releases "nontoxic, oxidized forms of sulfur which are excreted primarily by the kidney". However, because of the inability of methemoglobin to carry oxygen, nitrite administration might contribute to the preexisting H2S-induced cellular hypoxia. Efficacy of nitrite for H2S toxicosis has not been critically examined or demonstrated in animals but it has been successful in the resuscitation of several human H2S victims.

---

**Aminoglycoside Antibiotics and Skeletal Muscle Relaxants**

<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 Primarily Cause Respiratory Paralysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>All species</td>
<td>Minutes to hours</td>
<td>Hours to 2 days; may be lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Sources**

The aminoglycoside antibiotics kanamycin, tobramycin, gentamicin, neomycin, and streptomycin have all been shown to produce a neuromuscular blockade which may enhance the blockade of skeletal muscle relaxants. Other antibiotics which have been implicated in neuromuscular blockade include penicillin G and V, tetracycline, and polymyxin A and B.

**Mechanism of Action**

- Aminoglycoside antibiotics have several possible modes of action including postsynaptic receptor blockade,
inhibition of acetylcholine release from nerve terminal, or local anesthetic-type of action.

- **Nerve terminal**-penicillin effect (which occurs only at massive doses) resembles anticholinesterase in action on the nerve terminal, producing prolonged negative after potential. May affect membrane sodium conductance.
- Polymyxins produce neuromuscular blockade (NMB) of complex and incompletely understood origin. Studies indicate postsynaptic site of action.
  
  **Note** - 4-aminopyridine can reverse NMB experimentally produced by polymyxins.
- The nephrotoxicity of gentamicin has been attributed to inhibition of phospholipases in lysosomes which results in a lysosomal storage disease.

**Signs**

- Onset between administration of last dose of antibiotic and onset of clinical symptoms has been reported from 1 - 26 hours.
- Human patients with myasthenia gravis appear at higher risk.
- The syndrome is well documented in man. Respiratory paralysis may occur from the use of aminoglycoside antibiotics alone or from the combination with surgical use of neuromuscular blocking agents.
- The antibiotic may cause such effects after administration by a variety of routes including: intramuscular, intravenous, subcutaneously, intraperitoneal, intrapleural, oral, and possibly others.
- Similar respiratory paralysis has been reported in a bird following an IM injection of gentamicin.
- Longer term exposure to aminoglycosides can cause renal failure.

**Lesions**

With renal failure, the epithelium of the proximal tubule (P3 segment) tends to be damaged.

**Prevention**

Prevention of the problem is the best approach. Aminoglycoside antibiotics should be administered only with extreme caution during surgery or in the postoperative period since the effect of surgical neuromuscular blocking agents may be enhanced.

**Treatment**

- Most life-threatening sign is hypoventilation.
  - Support of ventilation is essential.
- Treatment with calcium or anticholinesterase agents (neostigmine) has been associated with a degree of improvement in some cases.
- **In vitro**, the NMB and associated paralysis produced by streptomycin, kanamycin, and gentamycin is reversed (> 70%) by administration of calcium. Calcium has only slight effect on lincomycin and no effect on polymixin NMB.
- Calcium chloride or calcium gluconate may be administered IV. Calcium infusion should be performed slowly and with EKG monitoring for arrhythmias.
- Generally, neostigmine is less effective in reversing antibiotic-associated NMB.
- 4-aminopyridine has had some success **in vitro** in reversing antibiotic NMB.
  - **Note** - Gentamicin also can be directly cardiotoxic.

**References**

**Hydrogen Sulfide (H2S)**

Aminoglycoside Antibiotics and Skeletal Muscle Relaxants


All rights reserved. This document is available on-line at www.ivis.org. Document No. A2611.0899.