

Central
New York
Regional
Poison
Control
Center

The CNYPC

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Toxicology Letter

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SCHEDULED EVENTS:

Emergency Medicine Grand Rounds
Health Sciences Library Room 318
Second Wednesday of the Month, 11:00 AM

January 10, 2001
February 14, 2001
March 14, 2001

Toxicology Case Conference
CNYPC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 1:30 PM – 2:30 PM

PROGRAM ANNOUNCEMENT:

We hope you all enjoyed the Fourth Annual Toxicology Teaching Day. If you would like a syllabus, please call 315-464-7078. Information on our Fifth Annual Toxicology Teaching Day will be coming shortly. Stay Tuned.

CNYPC TIDBITS:

1. A potassium of \geq (____) indicates a potential for lethality after ACUTE digoxin overdose.
2. Potassium does not have prognostic value after CHRONIC digoxin overdose. (True/False)
3. Digoxin level after the administration of digoxin specific Fab fragments is of no value as it is measuring both free digoxin and digoxin bound to digoxin specific Fab fragments. (True/False)

TOX TRIVIA:

Match the toxin with the major organ affected

- | | |
|-------------------------|-----------|
| 1. Toluene | A. Kidney |
| 2. Carbon tetrachloride | B. Heart |
| 3. Chronic ipecac | C. Liver |

Case History

Contributed by: Jayne Healey, M.D.
Christine M. Stork, Pharm.D. DABAT.

BREATHLESS FARMERS AND HOCKEY PLAYERS

Case:

A 54 year old previously healthy male presented to the emergency department complaining of 4 hours of increasing dyspnea. Initial vital signs included a temperature of 102° F, heart rate of 90/minute, blood pressure of 130/80 mmHg, respiratory rate of 30/minute, and pulse oximetry of 93% on 3 liters/minute of supplemental oxygen by nasal cannula. The physical examination was significant for rales in the lower two-thirds of the lungs bilaterally. An arterial blood gas (ABG) analysis revealed a pH of 7.40, pCO₂ of 38, pO₂ of 66, base excess of negative 23, and an A-a gradient of 0.45 on 3 liters nasal cannula. The patient subsequently vomited and became hypotensive, requiring IV fluid resuscitation. History revealed that he had been working in his silo earlier in the day.

What is "Silo Filler's disease"?

"Silo filler's disease" is a term used to describe a syndrome of acute pulmonary toxicity experienced by farmers exposed to high levels of nitrogen dioxide (NO₂) while working in silos. Silos that house decomposing fertilizer accumulate toxic levels of nitrogen dioxide if not properly ventilated. At very high levels, the gas is seen as a reddish-brown haze and has a bleach-like odor. Due to its low water solubility, nitrogen dioxide is only mildly irritating to the upper airways, therefore prolonged exposure and inhalation deep within the lungs is possible. Symptoms are typically delayed and consist of cough, dyspnea, chest pain, nausea, and vomiting. Patients often present with hypoxia and may appear cyanotic. Nitrogen dioxide has direct toxicity against pulmonary tissues, reducing available surfactant. Nitrogen dioxide also generates free radicals, causing further alveolar injury. In addition, dissolution of NO₂ in the water of the respiratory tract forms nitric and nitrous acids, also damaging to pulmonary tissues. Significant exposure results in pulmonary edema and pneumonitis. In a small subset of patients, enough NO₂ is converted to nitrates to cause methemoglobinemia. Chest x-rays in exposed patients reveal diffuse infiltrates in a miliary pattern or confluent opacities consistent with pulmonary edema.

Where else is nitrogen dioxide found?

Nitrogen dioxide is found in detectable levels as a result of air pollution and may contribute to chronic lung diseases such as asthma. It is a byproduct of welding and brazing processes and is also

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produced during the burning of radiographic film. Patients trapped in closed-space fires may have significant exposures to NO₂. Interestingly, ice-cleaning machines, such as the Zamboni, oxidize propane and produce NO₂ as an end-product. The enclosed space of an ice arena may become a dangerous source of NO₂ exposure. Several literature reports cite cases of hockey players developing pulmonary symptoms consistent with NO₂ toxicity after prolonged periods of time spent in ice arenas maintained by Zambonis.

What are some other toxic gases?

Toxic gases are categorized into two large groups. The simple asphyxiant gases generally possess no direct toxicity but simply reduce the partial pressure of available oxygen by displacement, lowering the concentration to less than 21%. The ultimate effect of these gases is to induce hypoxemia in poisoned patients. Treatment consists of removal from exposure, supplemental oxygen, and ventilatory assistance, if necessary. Gases falling into this category include: the noble gases helium, neon, argon, and xenon; hydrocarbons such as methane, ethane, propane, and butane; and also carbon dioxide and nitrogen.

The irritant gases, in addition to displacing oxygen, cause direct damage to the respiratory tract. Whereas asphyxiant gases are more insidious in their presentation of progressive dyspnea, irritant gases often cause immediate symptoms related to mucosal irritation. Rapidity of onset of symptoms is related to the hydrophilic nature of the individual gases, as will be discussed below. Hypoxemia results, not from reduction of pO₂, but from destruction of pulmonary tissues with subsequent compromise of gas exchange.

What are the irritant gases - and how are they classified?

Irritant gases require dissolution in mucosal water in order to exert their toxic effects. The water solubility of an irritant gas determines its likelihood of causing pulmonary damage. Highly water soluble gases dissolve rapidly and cause immediate symptoms of conjunctival, nasal, oral, and pharyngeal irritation. Victims tend to remove themselves promptly from exposure and avoid inhalation deep within the lungs. These agents typically produce only upper respiratory tract damage. Exceptions occur when patients are exposed to very high concentrations or if there is a delay in escape.

Gases with very low water solubility are less rapidly irritating, and patients may not recognize symptoms until significant exposure has occurred. Prolonged breathing of the irritant gas increases not only the level of exposure but also the depth of entry into the bronchopulmonary system. Inflammatory responses to these agents consist

(CONT.)

of tracheobronchitis, bronchiolitis, and pulmonary edema. When alveolar damage with subsequent impaired diffusion capacity occurs, patients exhibit significant morbidity and mortality.

What are the clinical manifestations of exposure?

Patients exposed to highly water soluble irritant gases may present with pain and mucosal edema of the eyes, nose, and throat, chemosis, drooling, cough, and stridor. Dermatologic irritation is also common with this group. These symptoms are typically immediate in onset after exposure.

Gases with intermediate water solubility share characteristics with gases of both the low and high water solubility groups. They produce less rapid mucosal irritation, thus inhalation further into the bronchopulmonary system is possible. Symptoms of both upper and lower respiratory tract irritation (throat pain, cough, dyspnea, etc) tend to progress over 6-8 hours.

Victims of poisoning with gases of low water solubility present less acutely but have a higher risk of progression to more serious disease. Initial symptoms may consist only of mild dyspnea and cough. Delayed symptomatology includes extreme dyspnea, chest pain, nausea and vomiting, and cyanosis. On physical exam, rales or wheezes can be noted. Pulse oximetry and laboratory analysis may reveal severe hypoxemia. Chest x-rays may show diffuse interstitial infiltrates or an alveolar pattern consistent with pulmonary edema. The most severe and dreaded form of this injury is acute respiratory distress syndrome (ARDS). Mortality from this syndrome is as high as 30%.

What is the initial patient management?

With any of the irritant gas exposures, immediate removal from the source is critical. No "antidote" exists for any of these agents, and treatment remains primarily supportive. Any patient with significant exposure should be admitted to the hospital for observation, despite initial mild symptomatology. Progression to more severe disease should be anticipated. Supplemental oxygen is recommended for all irritant gas exposures. Bronchodilation with inhaled β -agonists is useful in relieving bronchospasm. Patients who fatigue or are unable to maintain their oxygenation should be intubated with mechanically assisted ventilation.

Victims with brief exposures to irritant gases with high water solubility, after initial management, require no further medical treatment. Symptoms are self-limiting, and delayed manifestations are not typical.

Patients with toxic inhalations of intermediate solubility gases warrant observation for 6-8 hours after exposure. They may initially present with mild clinical manifestations

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but later progress to more severe symptomatology. Some agents, such as chlorine gas, are converted to acids on exposure to water and are extremely caustic to mucosal tissues. Aerosolized sodium bicarbonate, diluted to 2%, is warranted if symptoms of irritation persist.

Treatment of low water solubility irritant gas poisoning consists of ensuring adequate oxygenation and ventilation, as described above. All patients should be admitted to the hospital for observation, as symptoms are likely to progress over 12-24 hours. Corticosteroids are controversial but are shown to be of some benefit in select patients. Methemoglobinemia resulting from nitrogen dioxide conversion to nitrates is treated with methylene blue. Possible late sequelae of toxic exposure are fibrotic changes in damaged airways resulting in bronchiolitis obliterans. Here, patients present 2-6 weeks after initial exposure with signs and symptoms similar to their initial presentation. Corticosteroids may be beneficial in preventing and treating these complications

Ensure adequate patient follow-up.

Patients must be counseled to follow up closely with their primary medical doctor after significant exposure to low water solubility irritant gases. As mentioned previously, inflammatory responses in the pulmonary tissues may result in delayed sequelae of fibrotic changes in the lungs. Patients should be made aware that there could be a latent phase of 2-6 weeks during which they are asymptomatic, followed by acute relapse of symptoms similar to their initial presentation. They should be instructed to seek medical care for recurrence of dyspnea, cough, and/or fever. Bronchiolitis obliterans and pulmonary edema are also possible after the latent phase, even despite initial mild clinical manifestations. Again, corticosteroids are controversial but may be helpful in preventing long-term pulmonary fibrosis.

Maintaining a high index of suspicion.

A high index of clinical suspicion is required when assessing patients with acute onset of dyspnea. Otherwise healthy patients with no past medical history of pulmonary disease warrant evaluation for possible toxic gas poisoning. Eliciting an in depth history may reveal

CNYPCC Tidbits answers:

1. 5 mEq/L (100% fatality if greater than 5.5 mEq/L)
2. True
3. True

Tox Trivia answers:

1. A
2. C
3. B

(CONT.)

exposure that the patient is unaware of. During the fall and winter months, awareness of common irritant gases may yield a diagnosis when the history doesn't seem contributory. As the title suggests, farmers filling silos and hockey players exposed to Zamboni fumes typically present in the fall or winter with acute onset of dyspnea. In these cases, keep nitrogen dioxide on the list of differential diagnoses while ruling out other cardiac and pulmonary etiologies.

Case follow-up.

The patient was admitted to the ICU and continued to require O₂ at 3 L/min by nasal cannula in order to keep pulse oximetry above 90%, but he never required intubation or mechanical ventilation. His vital signs corrected to a temperature of 99.2o F, heart rate of 79/minute, blood pressure of 120/80, and respiratory rate of 18/minute. The next day his lung exam revealed only moderate bibasilar rales, he no longer required supplemental oxygen, and his chest x-ray showed resolving interstitial edema. The patient was able to be discharged home after 2 days, but close follow-up with his physician for several weeks was recommended in order to monitor for late sequelae.

Table 1. Classification of common irritant gases - solubility in water

High Solubility	Intermediate Solubility	Low Solubility
Chloramine	Chlorine	Phosgene
Ammonia	Ozone	Nitrogen dioxide

Suggested Reading:

1. Anonymous. Ice hockey lung: NO₂ poisoning. Lancet. 1990; 335(8699):1191.
2. Douglas, WW, Hepper, NG, Colby, TV. Silo-filler's disease. Mayo Clinic Proceedings. 1989; 64(3):291-304.
3. Goldfrank, et al. Toxicologic Emergencies, 6th ed.. 1998. Chapters 94 and 110.
4. Karlson-Stiber, C, Hojer, J, Sjöholm, A, Bluhm, G, Salmonson, H. Nitrogen dioxide pneumonitis in ice hockey players. Journal of Internal Medicine. 1996; 239(5):451-6.
5. Rorison, DG, McPherson, SJ. Acute toxic inhalations. Emergency Medicine Clinics of North America. 1992; 10(2):409-35.
6. Zwemer, FL, Jr, Pratt, DS, May, JJ. Silo filler's disease in New York State. American Review of respiratory Disease. 1992; 146(3):650-3.

SPI CORNER TOPIC: NEWSWORTHY FDA CHANGES

Contributed by: Marvleen Hollenbeck, R.N. CSPI

Troglitazone

In March 2000, the manufacturer of Rezulin ® (troglitazone) was asked by the FDA to remove this drug from the market. Parke-Davis/Warner-Lambert agreed to the request. This action was based on the FDA's review of safety data on Rezulin ®, a drug used to treat type 2 diabetes. Two similar drugs, rosiglitazone (Avandia®) and pioglitazone (Actos®) were also investigated, but it was found these two were less toxic to the liver than Rezulin ®. Recent safety data demonstrates that Actos ® and Avandia ® offer the same benefits as Rezulin ® but not the same risks.

Since 1997, Rezulin ® has been known to cause severe liver toxicity. At that time, Park-Davis strengthened the label warning and advised close monitoring of liver function in patients on Rezulin ®. The adverse effects were studied and it was made clear that the newer drugs had less risk of liver toxicity.

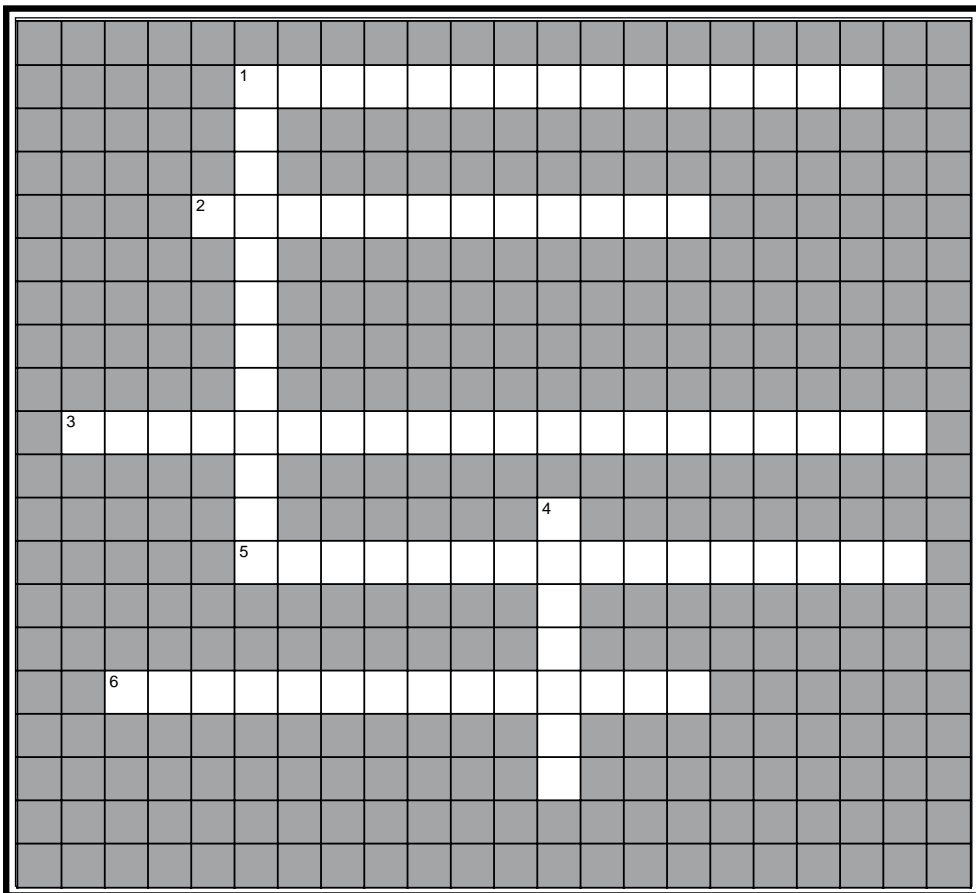
Phenylpropanolamine (PPA)

On November 6, 2000, the Food and Drug Administration (FDA) produced a public health advisory concerning the risk of hemorrhagic stroke while using

phenylpropanolamine hydrochloride. It is now requested that drug companies discontinue marketing products containing PPA. This drug is an ingredient in many over-the-counter cold and cough medications and also in OTC weight loss products.

The new warning was issued based on information that was provided to the FDA from scientists at Yale University School of Medicine. Their report entitled "Phenylpropanolamine and Risk of Hemorrhagic Stroke: Final Report of the Hemorrhagic Stroke Project" found that women had an increased risk of stroke but men may also be at risk after PPA use.

The FDA plans to remove PPA as an ingredient in over-the-counter and prescription drug products but until then recommends that consumers not use any products use products that contain PPA. It is included in such brand name products as Triaminic ®, Dimetapp ®, Coricidin ®, Contac Maximum Strength ®, Comtrex ®, Tavist-D ®, Triaminicol Multi-Symptom ®, Acutrim ®, Dexatrim ® and Stay Trim Diet Gum ®, along with many others. Local stores have started pulling these products from their shelves. If possible, many of these products may be reformulated without PPA and then returned to the market.



DRUGS CAUSING TACHYCARDIA

Contributed by:
Teesh Guenther, RN, CSPI

Across:

1. Diphenhydramine, antipsychotics, antispasmodics, some plants
2. Bronchodilator, COPD treatment
3. Examples: imipramine, doxepin
5. albuterol, epinephrine, cocaine
6. examples: Mellaril ®, Serentil ®, Prolixin ®

Down

1. used for ADD, used for weight loss
3. "nicknames" crack, snow

Across: 1. anticholinergic; 2. theophylline; 3. cyclic antidepressants; 5. sympathomimetics; 6. phenothiazines
Down: 1. amphetamines; 4. cocaine