New York State Poison Centers
1-800-222-1222

April 2004

The NY State Poison Centers

TOXICOLOGY LETTER

A Quarterly Publication • Vol. IX No. 2

Toxicology Advice Centers • •

Administrative Phone Numbers - To obtain a consult in your area, call 1.800.222.1222.

Western New York Poison Center (WNY)

716.878.7871 • www.chob.edu / poison

Finger Lakes Regional Poison & Drug Info Center (FL)

585.273.4155 • stronghealth.com / services / poison / index.cfm

Central New York Poison Center (CNY)

315.464.7078 • www.cnypoison.org

New York City Poison Control Center (NYC)

212.447.8152

Long Island Poison & Drug Info Center (LI)

516.663.4574 • www.LIRPDIC.org

Program Announcements • •

FL: Conference, Thursdays • 1:00-2:00pm

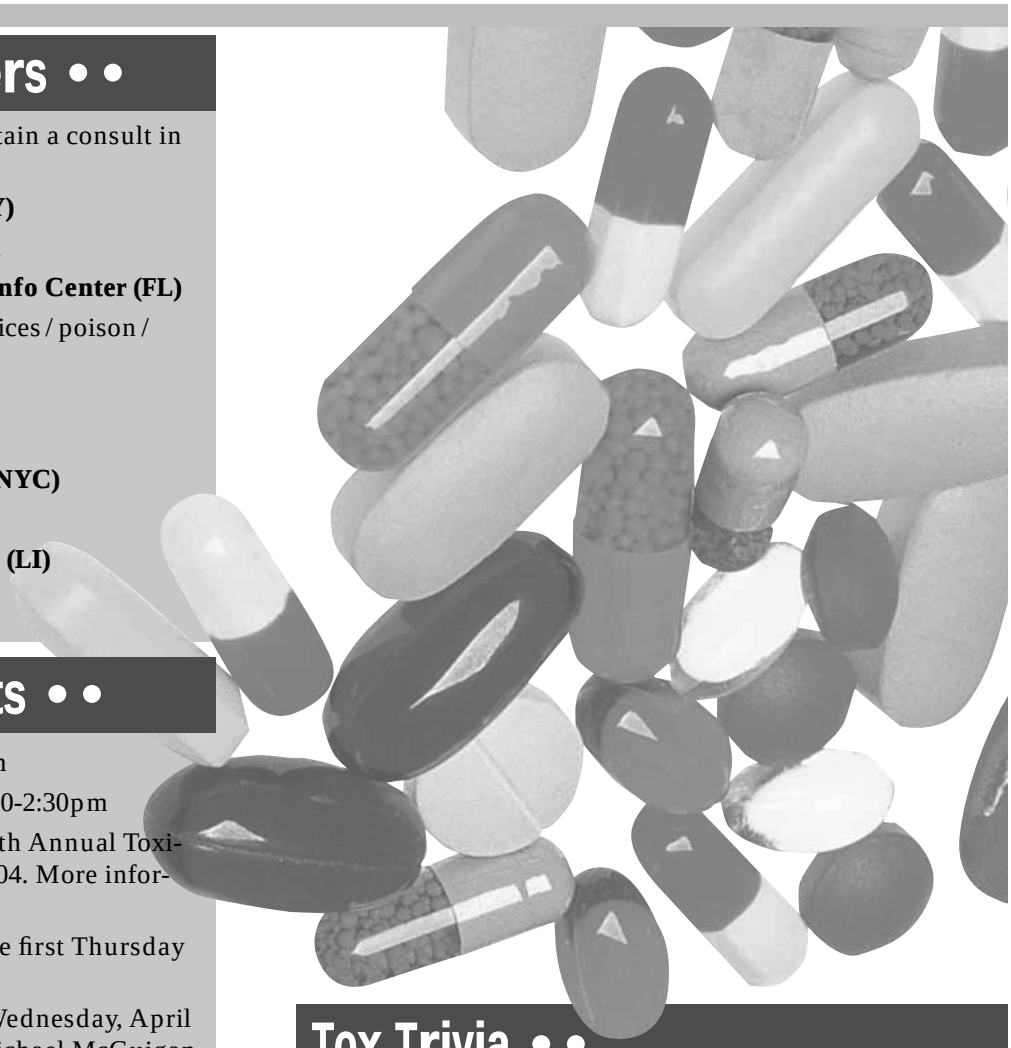
CNY: Case Conferences, Thursdays • 1:30-2:30pm

Please mark your calendars for the Eighth Annual Toxicology Teaching Day on November 3, 2004. More information to follow...

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

LI: *Polymorphism and Acute Toxicology* • Wednesday, April 28,2004 • 12:15-2:00pm • Speaker: Dr. Michael McGuigan • WUH New Life Center Conf Rms B & C
Heavy Metal Toxicity • Wednesday, May 26,2004 • 12:15-2:00PM • Speaker: Dr. Howard Mofenson• WUH New Life Center Conf Rms B & C
Dangerous Drug Interactions • Wednesday, June 23, 2004 • 12:15-2:00PM • Speaker: Dr. David Juurlink • WUH New Life Center Conf Rms B & C
Pre-Registration is required. Please contact T Caraccio at 516-663-2650 if interested in attending.
Televideo conferences can be arranged with institutions.

Please call administrative telephone numbers for more information.



Tox Trivia • •

1. On October 26,2002, what type of gas was used by the Russian government to end the hostage crisis by Chechen rebels in Moscow?
2. On October 15,2003 what toxic chemical was identified in an envelope found at a mail processing center in Greensville, South Carolina?
3. What toxin was mixed with fruit punch in the 1978 Jonestown mass suicide poisonings in Guyana, resulting in the deaths of more than 900 people?
4. In 1995 which toxic agent was released in the Tokyo subway system?

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FDA Safety Summaries 10/03 - 3/04

- **Duragesic (fentanyl transdermal system)**

  A potential seal breach on one edge may allow drug to leak from the patch and could result in an increased absorption of the opioid component, fentanyl, leading to increased drug effect, including nausea, sedation, drowsiness, or potentially life threatening complications. Conversely, if the hydrogel contents leak out of the patch, there may not be adequate medication to treat the patients' pain. Feb 17, 2004

- **Counterfeit contraceptive patches**

  FDA and Johnson and Johnson Co. of Raritan, NJ are warning the public about an overseas internet site selling counterfeit contraceptive patches that contain no active ingredients. February 4, 2004

- **Viramune (nevirapine)**

  Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with VIRAMUNE. February 2004

- **Antibody to HBsAg ELISA Test System 3**
- **Antibody to HBsAg ELISA Test System 3 Confirmatory Test**

  Ortho-Clinical Diagnostics Inc. and FDA notified healthcare professionals of reports of increased initial reactive (IR) and repeat reactive (RR) rates obtained with the Antibody to HBsAg ELISA Test System 3 donor screening assay, with false repeat reactive results being confirmed using the Antibody to HBsAg ELISA Test System 3 Confirmatory Test. December 23, 2003

- **Tamiflu (oseltamivir phosphate) Capsules and for Oral Suspension**

  Preclinical findings in juvenile rats have raised concerns regarding the use of Tamiflu in infants less than 1 year of age. A single dose of 1000 mg/kg oseltamivir phosphate (about 250 times the recommended dose in children) in 7-day-old rats resulted in deaths associated with levels of oseltamivir phosphate in the brain approximately 1500 times those seen in adult animals. December 2003

- **Topamax (topiramate) Tablets/Sprinkle Capsules**

  Topamax causes hyperchloremic, non-anion gap metabolic acidosis (decreased serum bicarbonate).December 2003

- **Permax (pergolide mesylate)**

  FDA and Lilly modified the WARNINGS and PRECAUTIONS sections to inform healthcare professionals of the possibility of patients falling asleep while performing daily activities,

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Chemical Agents of Opportunity by Terrorists

Case History:

Contributed By: *T Caraccio, Pharm.D.*, Salamati A, Pharm.D. Candidate+, Varghese, Pharm.D. Candidate J+, Sakai J, Pharm.D. Candidate +*

Long Island Regional Poison and Drug Information Center and St John's University College of Pharmacy and Allied Health Professions

Case Summary:

On March 30, 1995, Shoko Asahara, a cult leader of Aum Shinrikyo, released a nerve agent in 5 subway cars on 3 separate subway lines in Tokyo. Nearly 6,000 were injured with 12 fatalities(1). Ten percent of pre-hospital personnel including police and paramedics experienced symptoms of nerve agent poisoning and as many as 46% of the hospital staff became symptomatic through improper handling of victims. This episode along with the recent events of the terrorist attacks on 911 in the United States has heightened concerns about chemical agents that may be used in a similar manor on civilian populations.

The purpose of this newsletter is to review the types of common agents, health effects and managements for chemical exposures that may be associated with acts of terrorism. We will emphasize recognition of four classical syndromes or toxidromes that are applicable to the deliberate release of chemicals as in acts of chemical terrorism. The classes of substances that correspond to these clinical syndromes are cholinesterase inhibitors (e.g., organophosphorus nerve agents), respiratory tract irritants (e.g., chlorine and phosgene), asphyxiants (e.g., cyanide), and vesicants (e.g., mustard).

How do accidental industrial releases of chemicals differ than deliberate release as in acts of chemical or biological terrorism?

In accidental industrial releases, information about the presence of specific chemicals may be available from the personnel of the facility, safety officials, and other sources. In contrast, an act of terrorism is more likely to involve substances that cannot be immediately identified. Owing to the rapidity of the onset of similar symptoms in a group of persons or the close proximity of a group of persons to a release of hazardous materials, chemical exposures are more quickly recognizable than are exposures to biologic agents (2). However, in contrast to the period of latency that is associated with the effects of biologic agents, when serious chemical intoxication occurs, the window for effective therapy is often narrow. Furthermore, real-time identification of specific chemicals by means of environmental or clinical laboratory testing is difficult (3).

Nerve Agents: What are they and how do they produce toxicity?

Like organophosphate insecticides, nerve agents phosphorylate and inactivate acetylcholinesterase, leading to accumulation of acetylcholine at nicotinic and muscarinic receptors, and at other receptors in the CNS. Nerve agents that have been used in chemical weapons include tabun (GA), sarin (GB), soman (GD), cyclosarin (GF) and VX.

What are the Properties of Nerve Agents?

At room temperature, all except VX are volatile. VX has the consistency of motor oil and becomes volatile only at high ambient temperatures. Nerve agent vapors are denser than air and tend to accumulate in low-lying areas. All nerve agents are lipophilic and hydrophilic, rapidly penetrating clothing, skin and mucous membranes.

What Clinical effects can be produced?

Exposure to a liquid or vapor nerve agent produces dose-dependent peripheral and CNS effects (4). Respiratory effects include rhinorrhea, bronchorrhea and bronchospasm (muscarinic), respiratory muscle paralysis (nicotinic) and depression of CNS respiratory drive. Cardiovascular effects include bradycardia and heart block (muscarinic) or tachycardia (nicotinic). CNS effects range from headache, agitation and vertigo, to rapidly decreasing level of consciousness and seizures. Peripheral motor effects include initial fasciculations followed by flaccid paralysis (nicotinic). Gastrointestinal effects include nausea, vomiting and diarrhea (muscarinic). Ocular effects include miosis, eye pain, blurred vision, dim vision, conjunctival injection and tearing (muscarinic) (5).

When are symptoms expected with Liquid Nerve agents?

Dermal exposure to a large dose of liquid nerve agent may be transiently asymptomatic (10-30 minutes), followed by rapid onset of respiratory and neurologic effects.With dermal exposure to a minimal amount of nerve agent liquid, the onset of localized symptoms (sweating, fasciculations) may be delayed for up to 18 hours.

When are symptoms expected with Vapor exposures?

Inhalation of a large amount of nerve agent vapor causes fulminant respiratory failure within seconds to minutes. Exposure to a small amount of vapor typi-

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cally produces more limited ocular (miosis, eye pain) and airway (hypersecretion, bronchospasm) effects.

How should decontamination be provided?

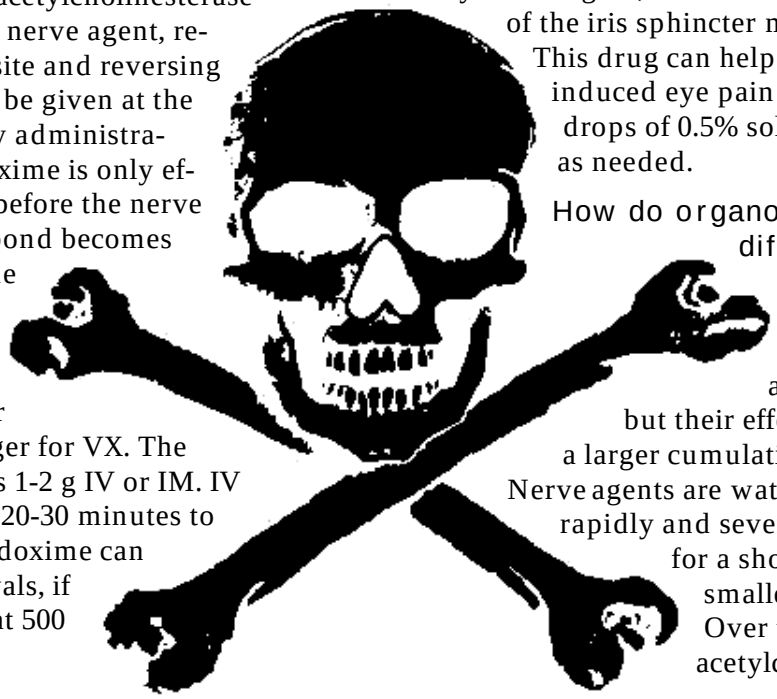
Patients exposed to liquid nerve agent require immediate decontamination to prevent further absorption. Decontamination consists of rapid removal of clothing and jewelry, followed immediately by irrigation with tepid water and washing with soap and water. If water is limited or unavailable, 0.5% hypochlorite solution, which inactivates nerve agents, can be helpful (6).

What Antidotes are recommended?

Even in severe cases of nerve gas exposure, treatment with antidotes can be life-saving (7).

Atropine: Atropine is a competitive inhibitor of acetylcholine at muscarinic receptors that reverses the hypersecretory, bronchoconstrictive and gastrointestinal effects of nerve agents. The usual adult dose of atropine is 2 mg IM for mild dyspnea and 6 mg for severe dyspnea. Appropriate therapeutic end points are drying of secretions and ease of ventilation. Heart rate and pupil size are poor clinical indicators of adequate atropinization, since tachycardia may reflect hypoxemia, stress or severe nicotinic effects, and miosis may persist for weeks. Repeat 2-mg doses can be given every 5-10 minutes; patients with nerve agent exposure rarely require more than 20 mg of atropine in the first 24 hours.

Pralidoxime Chloride: . Pralidoxime chloride *(Protopam Chloride)* is an oxime acetylcholinesterase reactivator that binds to the nerve agent, removing it from its binding site and reversing muscle weakness. It should be given at the same time as atropine. Early administration is critical, since pralidoxime is only effective when administered before the nerve agent acetylcholinesterase bond becomes permanent ("ages"); the time it takes for half of the nerve agent to "age" is about 2 minutes for Soman, 5 hours for Sarin, 13 hours for Tabun, and 48 hours or longer for VX. The usual dose of pralidoxime is 1-2 g IV or IM. IV doses should be given over 20-30 minutes to prevent hypertension. Pralidoxime can be repeated at hourly intervals, if necessary, or continuously at 500 mg / hour by IV infusion.



Auto-Injectors: Spring-loaded auto-injectors for IM use containing (separately) atropine 2 mg, pralidoxime 600 mg, diazepam 10 mg and morphine 10 mg are available from Meridian Medical Technologies, Columbia, MD (www.meridianmeds.com / civdef.html).

Diazepam: Early administration of the anticonvulsant diazepam (*Valium*), 10 mg IM may prevent permanent CNS damage in patients with severe nerve agent toxicity.

What is the rationale for using Pyridostigmine for a Nerve agent exposure?

Pyridostigmine bromide (*Mestinon)* is an acetylcholinesterase inhibitor with a short half-life used in the treatment of myasthenia gravis. Since it can bind to peripheral acetylcholinesterase for several hours, it is useful because it can temporarily block inactivation by a nerve agent. Pyridostigmine itself does not counteract the effects of the nerve agents; it only **enhances** the effects of antidotes. The usual adult dose is 30 mg PO q8h. (8). If there is a risk of imminent exposure, one dose of pyridostigmine at least 2 hours before may be helpful; 2 doses 8 hours apart are preferable. In animal studies, pretreatment with pyridostigmine has been effective against Tabun or Soman, ineffective against Sarin or VX, and variably effective against Cyclosarin, depending on the species.

What ocular medication may be useful for these exposures?

Tropicamide (*Mydriacyl),* is a topical cycloplegic-mydriatic agent, that blocks cholinergic stimulation of the iris sphincter muscle and ciliary body. This drug can help in relieving nerve-agent induced eye pain (9). The adult dose is 1-2 drops of 0.5% solution in each eye, repeated as needed.

How do organophosphate insecticides differ from Nerve agents?

Organic phosphorus insecticides are oily, less volatile liquids. They have a slower onset of toxicity, but their effects last longer and require a larger cumulative dose of atropine (10). Nerve agents are watery and volatile, acting rapidly and severely, but their effects last for a shorter time and require a smaller total dose of atropine (11). Over time, organophosphorus–acetylcholinesterase binding

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becomes irreversibly covalent and resistant to reactivation by pralidoxime, in a process known as "aging." Aging has clinical implications for Soman, which ages in minutes, and Sarin, which ages over a period of three to five hours (12). Pralidoxime should never be withheld, however, out of concern that it might be administered too late after exposure. For organophosphorus insecticides, aging is not clinically relevant because these agents age at a slow rate (13). Among nerve agents, VX has several unique characteristics. It is oily, is persistent in the environment, and ages minimally, but even one drop of the substance on the skin can be lethal (14).

How do Carbamate insecticides differ from Nerve agents?

Carbamate insecticides have a more limited penetration of the central nervous system, inhibit acetylcholinesterase reversibly, and result in a shorter, milder course than nerve agents. Nevertheless, in the treatment of severe cholinergic syndromes, it is prudent to use both atropine and pralidoxime (13).

Which Chemical agents might a terrorist utilize to produce Respiratory Irritation?

The pulmonary toxicants most likely to be used can include chlorine, phosgene and diphosgene. Other respiratory irritants are tear gas and lacrimators but these are generally considered weaker because because there duration of action is usually of a shorter and reversible nature especially in an open area.

What are the properties of these Respiratory Irritants?

Chlorine, phosgene and diphosgene exist as gases under ambient conditions. Diphosgene readily degrades to phosgene and nontoxic levels of chloroform. Pulmonary toxicants are denser than air and accumulate in low-lying areas. Chlorine, phosgene, and diphosgene all react with water to produce hydrochloric acid, which damages tissue, but phosgene also acylates amino, hydroxyl and sulfhydryl groups in tissue, causing a chain of oxidative injury. The most common sites of injury are mucous membranes such as the conjuctiva and respiratory tract, including the alveolar-capillary membrane.

What clinical effects can be produced?

Chlorine dissolves readily in the moist mucosa of the upper respiratory tract, producing rhinorrhea, hypersalivation and laryngeal edema, as well as lower respiratory tract reactions such as coughing, wheezing and rales (15).

Phosgene and diphosgene, which are relatively insoluble, pass further into the respiratory tract where they are more slowly absorbed, producing bronchoalveolar injury, dyspnea, bronchospasm and permeability pulmonary edema. Clinical effects of pulmonary toxicants vary with the concentration and duration of exposure. Low-dose inhalation causes minor pulmonary irritation and bronchospasm. High-dose inhalation may produce laryngospasm, pneumonitis and acute lung injury with acute respiratory distress syndrome (ARDS). The delayed onset of ARDS (up to 48 hours in initially asymptomatic patients) is characteristic of pulmonary toxicant inhalation.

The chemical agents used for riot control - tear gas or other "lacrimators" - are aerosolized solids that cause intense, immediate, and usually self-limited burning on exposed body surfaces, especially the eyes (16).

What Manangements should be provided?

Oxygen: Supplemental oxygen may improve tissue oxygenation in patients with pulmonary signs and symptoms. Airway or ventilatory compromise requires intubation. Ventilatory support management of ARDS requires positive end-expiratory pressure.

Bronchodilators: Beta2-adrenergic agonists relax airway smooth muscle, increasing airway diameter and reducing hyperactivity in pulmonary toxicant inhalation (17). The usual adult dose of albuterol (*Proventil*, and others) is 2.5 mg in 3 ml of sterile water, nebulized and repeated as needed. Theophylline may also be helpful (18).

Corticosteroids: Corticosteroids such as prednisolone have been used in an attempt to prevent pulmonary edema in the asymptomatic latency phase following phosgene inhalation. The dose of prednisolone has been 250 mg IV. A dose of 1 g IV has been recommended for treatment of phosgene-induced pulmonary edema (19). Whether it would also be helpful for chlorine inhalation is unknown.

Others: In animals, one or two large doses of ibuprofen decreased the toxicity of exposure to phosgene (20). An acetylcysteine aerosol, 20 ml of a 20% solution given by nebulizer, has also been effective in animals.

What are chemical Asphyxiants?

Asphyxiants are substances that cause tissue hypoxia with prominent neurologic and cardiovascular signs. Mild symptoms of asphyxia include headache, fatigue, dizziness, and nausea. More severe symptoms range from dyspnea, altered mental status, cardiac ischemia, and syncope to coma and seizure. Respira-

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tory failure, if it occurs, generally results from depression of the central nervous system. Asphyxiants are classified as either simple or chemical on the basis of the mechanism of toxicity. Simple asphyxiants (e.g., methane and nitrogen) physically displace oxygen in inspired air, and their inhalation results in oxygen deficiency and hypoxemia. Chemical asphyxiants (e.g., carbon monoxide, cyanide, and hydrogen sulfide) interfere with oxygen transport and cellular respiration and thereby cause tissue hypoxia.

Which asphyxiant is considered to be the most useful by a terrorist and why?

Cyanide (CN) is one of the oldest toxins known, and has killed millions throughout the ages. Few poisons are more rapidly lethal. It has been experimented with by the Islamic jihad in Israel and Al Queda in their training camps. It was used most recently as a tool of murder in January 2003 when a teenager was murdered by an acquaintance who laced his soft drink with potassium cyanide that was purchased over the internet. In 1982, Tylenol® capsules laced with cyanide killed 7 in Chicago area and led to the tamper proof packaging for medications that we have today. In November 1978, Potassium cyanide laced Kool Aid was used by Jim Jones to kill himself and 913 of his Jonestown Guyana Cult members. It was used in executions by the ancient Greeks, Egyptians and Romans and by Nazi Germany in gas chambers with Zyklon B to exterminate millions of Jews. The potential for industrial accidents involving cyanide, accidents during the shipment of these chemicals, or through deliberate terrorist acts upon industrial complexes or shipments of these chemicals is a major concern. There are a variety of the industrial processes and occupations that utilize cyanide including semiconductors, electroplating, photography, fumigation, and mining of ores. It is also produced by fires involving polyurethane, wool, cotton and silk. Cyanogenic glycosides in the seeds of fruit stones (as amygdalin in apricots, peaches, apples, peach) in the presence of intestinal β-glucosidase forms cyanide (the seeds are harmful only if the capsule is broken); Sodium nitroprusside, the antihypertensive vasodilator contains 5 cyanide groups.

What is the toxic mechanism?

Cyanide blocks cellular electron transport mechanism and cellular respiration by inhibiting the mitochondrial cytochrome oxidase system and other enzymes. This results in cellular hypoxia and lactic acidosis (21).

What is the toxic dose?

The ingestion of 1 mg/kg or 50 mg of hydrogen cyanide (HCN) can produce death within 15 minutes. The lethal dose of potassium cyanide is 200 mg. Five to 10 mL of 84% acetonitrile is lethal. The volatile HCN permissible exposure limit (PEL) is 10 ppm, 300 ppm is fatal in minutes.

What are the kinetics?

Cyanide is rapidly absorbed by all routes. In stomach it forms hydrocyanic acid. Protein binding is 60% and the volume of distribution is 1.5 L/kg. Cyanide is detoxified by metabolism in the liver via the mitochondrial endogenous thiosulfate-rhodanese pathway which catalyzes the transfer of sulfur donor to cyanide forming the less toxic irreversible thiocyanate that is excreted in the urine. Cyanide elimination half life from the blood is 1.2 hrs. Cyanide is also detoxified by reacting with hydroxocobalamin (vitamin B-12a) to form cyanocobalamin (vitamin B-12). The elimination route is through the lungs (22).

What are the manifestations of HCN?

Hydrogen cyanide has the distinctive odor of bitter almonds or silver polish, (only 30-40% of the population can detect the odor). The clinical findings develop rapidly and include: flushing, hypertension, headache, hyperpnea, seizures, stupor, cardiac dysrhythmias, pulmonary edema (22). Cyanosis is absent or appears late. Various ECG abnormalities may be present.

What Management should be provided?

Protect rescuers and attendants. Immediately administer 100% oxygen and continue during and after the administration of the antidote. If inhaled, remove patient from contaminated atmosphere. Attendants should not administer mouth-to-mouth resuscitation.

Cyanide antidote kit: The clinician must decide whether to use any or all components of the kit.

a) **The mechanism of action of the antidote kit** is to form methemoglobinemia (Methb) which has a greater affinity for cyanide than cytochrome oxidase system and forms cyanomethemoglobinemia. The cyanide is transferred from methemoglobinemia by sodium thiosulfate which provides a sulfur atom that is converted by the rhodanese-catalyzed enzyme reaction (thiosulfate sulfur transferase) to convert cyanide into the relatively non-toxic sodium thiocyanate which is excreted by the kidney (21-22).

b) **The Procedure for using the Antidote kit**: **Step 1 Amyl nitrite inhalant perles are** only a temporizing measure (forms only 2-5% Methb) and can be omitted if venous access is established. Administer 100% oxygen and the inhalant for

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30 seconds of every minute. Use a new perle every 3 minutes. **Step 2 Sodium nitrite ampul** is administered IV to produce Methb of 20-30% at 35-70 minutes after administration. In **adults,** administer 10 mL of 3% solution of sodium nitrite, **child** 0.33 mL / kg of 3% is diluted to 100 mL 0.9% saline **slowly** IV at 5 mL / min. If hypotension develops, slow the infusion. **Step 3** In **adults** administer12.5 grams of **sodium thiosulfate** or 50 mL of 25% solution, **child** 1.65 mL / kg of 25% solution IV over 10-20 minutes. Note: **Sodium thiosulfate is useful alone** in smoke inhalation, nitroprusside toxicity and acetonitrile toxicity.

c) If cyanide symptoms recur, repeat the IV antidotes in 30 minutes. Give 1/2 of the initial doses. The children dosage regime on the package insert must be carefully followed.

d) One hour after antidotes are administered, the Methb level should be obtained and should not exceed 20%. Methylene blue should **not** be used to reverse excessive Methb.

GI decontamination by activated charcoal is recommended for an oral ingestion but is not very effective (1 gram binds only 35 mg of cyanide).

Treat **seizures** with IV diazepam. Correct acidosis with sodium bicarbonate if it does not rapidly resolve with therapy.

Other antidotes. In France **hydroxocobalamin (vitamin B-12a)** which exchanges its hydroxyl with free cyanide to form cyanocobalamin is used (23). It has proven effective when given immediately after exposure in large doses of 4 grams (50 mg / kg) or 50 times the amount of cyanide exposure with sodium thiosulfate. Unfortunately the more concentrated form of hydroxocobalamin is not readily available in the US.

What laboratory investigations should be monitored?

Obtain and monitor ABGs, oxygen saturation, blood lactate, blood cyanide, hemoglobin, blood glucose, and electrolytes. Lactic acidemia, a decreased arterial-venous oxygen difference and bright red venous blood can occur.

What are Vesicants?

Vesicants are agents that were developed to produce "blisters" and burns on skin. Mustard gas was first used offensively by the Germans at Ypres, Belgium in July 1917. Typical agents include Sulfur mustard and Lewisite.

Properties: Mustards were named for their pungent mustard-garlic odor. Sulfur mustard, an oily liquid that vaporizes at high ambient temperatures, is the most common vesicant used in chemical weapons. Mustard is lipophilic and readily penetrates skin, most textiles and rubber. It irreversibly alkylates DNA, RNA and protein, causing cell death. Moist, warm tissues (mucosa, perineum, axillae) are most vulnerable, because the chemical reaction is water- and temperature-dependent.

Lewisite is a colorless oily liquid with the odor of geraniums. It is an arsenical derivative which is added to Mustard to keep it a liquid at temperatures below 57°F. As an arsenical, it can interfere with cellular enzymes.

What are the clinical effects of mustard?

Dermal exposure to liquid mustards causes burns that progress from superficial (erythema, pain) to partial thickness (bullae) and, uncommonly, to full thickness (deep bullae, ulcers). Skin contact with sulfur mustards may produce pain after a delay of minutes to hours. Inhalation exposure to mustard vapor can cause mucosal sloughing and airway obstruction. Ocular effects from exposure to liquid or vapor mustard range from ocular irritation and conjunctivitis to corneal burns and blindness. After exposure to high doses, bone marrow suppression can begin in 3-5 days, resulting in leukopenia that reaches its nadir around day 10, followed by thrombocytopenia and sometimes anemia. Nausea and vomiting are common 4-5 days post-exposure; diarrhea and bleeding can occur (24).

Lewisite can cause severe burns to the eyes and skin. Its effects occur faster (within minutes) compared to mustard (takes hours) and can result in larger and deeper burns. These burns can result in considerable necrosis of tissue, gangrene and slough. Respiratory lesions and ocular effects are similar to mustard.

What is the management?

Patients exposed to sulfur mustard require rapid removal of clothing, followed immediately by flushing with soap and water (25). Sloughing of the airway epithelium requires endotracheal intubation. Overhydration should be avoided; chemical burns produce less fluid loss than thermal burns. Mustard burns are especially painful and require liberal opioid analgesia. Severe burns usually require irrigation, debridement and topical antibiotics such as silver sulfadiazine 1% (26). Eye care includes irrigation, topical antibiotics and cycloplegic-mydriatics; application of petroleum jelly can prevent burned lids from sticking (27). Gran-

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Chemical Agents of Opportunity by Terrorists

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ulocyte colony-stimulating factor or filgrastim (*Neupogen)* can be used for treatment of mustard-induced neutropenia (28,29).

British Antilewisite or BAL in oil(10%), (Dimercaprol) can be given IM for the systemic effects produced by Lewisite. It acts to displace arsenic from its combination with sulhydryl groups of enzyme proteins.

Should civilians use Gas Masks?

Use of military gas masks by untrained civilians is not recommended; the usual full-face mask imposes a large respiratory load and excessive dead space. The ability of military gas masks (e.g., a US military M40 mask) to provide ocular and respiratory protection depends on the fit and the integrity of the filter canister, which can be damaged by handling, water and excessive breathing pressures and must be replaced every 30 days. In Israel during the Gulf War, improper use of gas masks by civilians resulted in 13 deaths due to suffocation (failure to remove the filter cap creates a negative-pressure suction effect that can make the masks difficult to take off), and a total of 114 people died from cardiorespiratory causes while using masks in sealed rooms (30).

References will be provided on request

Tox Trivia • •

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5. What chemical was launched by the Germans on the battlefield of Ypres, Belgium in April 1915?

6. What chemical was released by a Union Carbide plant in Bhopal India in December 1984 that caused injuries in tens of thousands of people and 3000 deaths?

7. What was the most toxic chemical used by the Germans in WWI that caused blisters on the skin, respiratory irritation and ocular injuries?

8. What was the name of the chemical used in the Nazi gas chambers in WWII?

9. What was the name of the chemical that was placed in a can of vanilla soda to kill a 17 year male in Maryland on January 6, 2003?

10. What was the toxin that the Russians used to kill Georgi Markov, a Bulgarian defector in 1978?

answers below

Tox Trivia Answers • •

1. Carfentanil, a fentanyl derivative 2. Ricin 3. Potassium Cyanide 4. Sarin nerve gas 5. Chlorine 6. Methylisocyanate 7. Mustad gas 8. Zyklon B or hydrogen cyanide pellets. 9. Potassium cyanide 10. Ricin

SPI CORNER TOPIC: RICIN

Contributed By: *Long Island Regional Poison and Drug Information Center Staff*

On October 15, 2003, an envelope containing ricin was found at a mail facility in Greenville, South Carolina. Many Poison Centers received questions about what this toxin is, what manifestations it could produce and what managements could be effective. The following is a brief review to answer these questions.

Ricin is a biologic toxin derived from the castor bean plant *Ricinus communis.* Ricin is one of several toxalbumins that exert toxicity by inhibiting protein synthesis in eukaryotic cells. Routes of exposure to ricin include ingestion, inhalation, parenteral, dermal, or ocular; however, systemic toxicity has been described in humans only after ingestion or injection. Ricin is considered to be a much more potent toxin when inhaled or injected compared with other routes of exposure. Ricin poisoning is not contagious, and person-to-person transmission does not occur.

Processed and purified ricin can be disseminated by aerosol, contamination of food or water, or injection. Data about the effects of ricin poisoning on humans are limited. Because ricin poisoning might resemble typical gastroenteritis or respiratory illness, it might at first be difficult to discern from other illnesses. For this reason, suspicion of cases should occur in conjunction with epidemiologic clues suggestive of chemical release (e.g., an unusual increase in the number of patients seeking care or unexpected progression of symptoms in a group of patients) or a credible threat of chemical release in the community.

Clinical Manifestations:

Ingestion: Signs and symptoms from oral exposure to purified ricin are presumed to be similar to reports of illness after castor bean mastication and ingestion. Toxicity can range from mild to severe and can progress to death. Mild illness can include nausea, vomiting, diarrhea, and / or abdominal cramping. Onset of gastrointestinal symptoms typically occurs in 1-4 hours. In moderate to severe illness, gastrointestinal symptoms (i.e., persistent vomiting and voluminous diarrhea [bloody or non-bloody]) typically lead to substantial fluid loss, resulting in dehydration and possibly hypovolemic shock. In severe poisoning, liver and renal failure and death are possible.

Inhalational Exposure: Workers exposed to castor bean dust have described allergic reactions (e.g., nasal and throat congestion, eye irritation, hives, chest tightness, and wheezing). Aerosol exposures to ricin can be followed within 4-8 hours by fever, chest tightness, cough, dyspnea, nausea, and arthralgias followed by diaphoresis.

Parenteral Exposure: In a single human trial evaluating low doses of intravenous ricin as a chemotherapeutic agent, influenza-like symptoms with fatigue and myalgias for several days were reported. Ricin injection in one case caused weakness within 5 hours, fever and vomiting within 24 hours, followed by shock and multiorgan failure, and death in 3 days.

Management: Treatment for ricin toxicity is primarily supportive, including intravenous fluids, vasopressors, respiratory support, and cardiac monitoring. No specific antidotal therapy exists, and ricin cannot be removed by dialysis. Prophylactic vaccine and immunotherapy are not available. A single dose of activated charcoal should be administered as soon as possible if the patient is suspected of ricin ingestion and is not vomiting. The efficacy of gastric lavage is controversial but may be considered for known or suspected substantial ingestions if presentation to the hospital occurs within 1 hour of ingestion. Ipecac, whole bowel irrigation, and cathartics should not be used.. Clinical presentations and their management can vary considerably. Clinicians are strongly advised to contact their regional poison control center immediately upon suspicion of a case of ricin exposure for guidance and further individualized management. Skin decontamination for ricin exposure should be performed if a powder or similar substance is found on the patient, preferably in a designated area outside the main emergency department. Potentially exposed persons should be advised to wash their hands thoroughly with soap and water and refrain from any hand-to-mouth activities.

Laboratory: Methods for the detection of ricin in biologic fluids are not commonly available. Ricinine is a separate compound from ricin present in the castor bean and might be more feasible to monitor in persons exposed to ricin-containing plant material. Preparations of ricin-containing substances and environmentally collected specimens can be tested for the presence of ricin by a time-resolved fluorescence immunoassay, available at CDC and member Laboratory Response Network state public health laboratories. In addition, CDC performs a polymerase chain reaction assay on similar type specimens that will detect the gene in the plant material that codes for the ricin protein. Several commercial handheld or test-strip detection devices are available, but the performance of these assays is unknown.

Reporting: Suspected or known cases of ricin poisoning should be reported immediately to the regional poison control center (telephone, 1-800-222-1222) and to local or state public health agencies, which will report cases to other health departments, CDC, and other federal agencies.

Continued from page 1

including operation of motor vehicles, while receiving treatment with Permax. December 15, 2003

- **Acetaminophen, Dixon's 325 mg Analgesic Tablets**

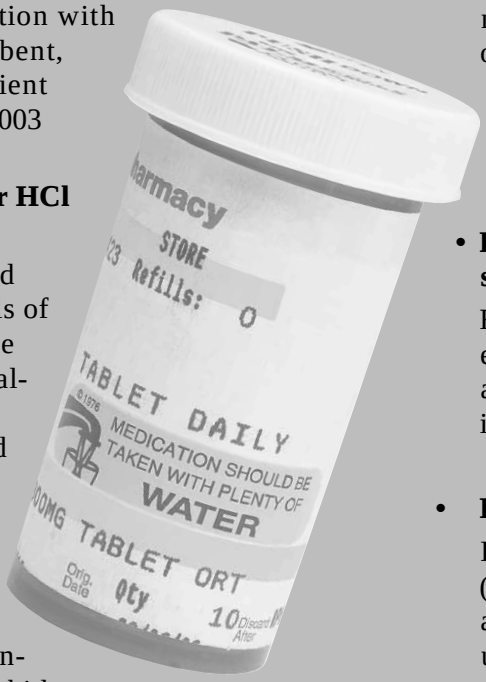
  The tablets contained in the mislabeled bottles are 500 mg Acetaminophen, instead of 325 mg Acetaminophen. December 4, 2003

- **Arava (leflunomide)**

  In postmarketing experience worldwide, rare, serious hepatic injury, including cases with fatal outcome, have been reported during treatment with Arava. October, 2003

- **Ultane (sevoflurane)**

  Reports of fire or extreme heat in the respiratory circuit of anesthesia machines when Ultane is used in conjunction with a desiccated CO_2 absorbent, which can result in patient injury. November 17, 2003



- **Valcyte (valganciclovir HCl tablets)**

  FDA and Roche notified healthcare professionals of the findings of an active comparator study of Valcyte and ganciclovir in heart, liver, kidney, and kidney-pancreas transplant patients at high risk for CMV disease. Based on those findings: (1) Valcyte is indicated for the prevention of CMV disease in kidney, heart, and kidney-pancreas transplant patients at high risk, (2) Valcyte is not indicated for use in liver transplant patients. September 30, 2003

- **Viread (tenofovir disoproxil fumarate)**

  High rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor (NRTI) resistance associated mutations observed in a clinical study of HIV-infected treatment-na ve patients receiving a once-daily triple NRTI regimen containing didanosine enteric coated beadlets (Videx EC, Bristol-Myers Squibb), lamivudine (Epivir, GlaxoSmithKline), and tenofovir disoproxil fumarate (Viread, Gilead).October 14, 2003

- **Keppra (levetiracetam) Tablets and Oral Solution**

  FDA and UCB Pharma advised healthcare professionals of the risk of dispensing errors between KEPPRA (levetiracetam), an antiepileptic, and KALETRA (lopinavir / ritonavir), an antiretroviral. September, 2003

- **Roxanol (morphine sulfate) Concentrated Oral Solution**

  Serious adverse events and deaths resulting from accidental overdose of high concentration morphine sulfate oral solutions. In most of these cases, morphine oral solutions ordered in milligrams (mg) were mistakenly interchanged for milliliters (mL) of the product, resulting in 20-fold overdoses. October 22, 2003

- **FD&C Blue No. 1 (Blue 1) in enteral feeding solutions**

  FDA alerted healthcare professionals of several reports of toxicity, including death, associated with the use of FD&C Blue No. 1 (Blue 1) in enteral feeding solutions. Sept 29, 2003

- **Prandin (repaglinide)**

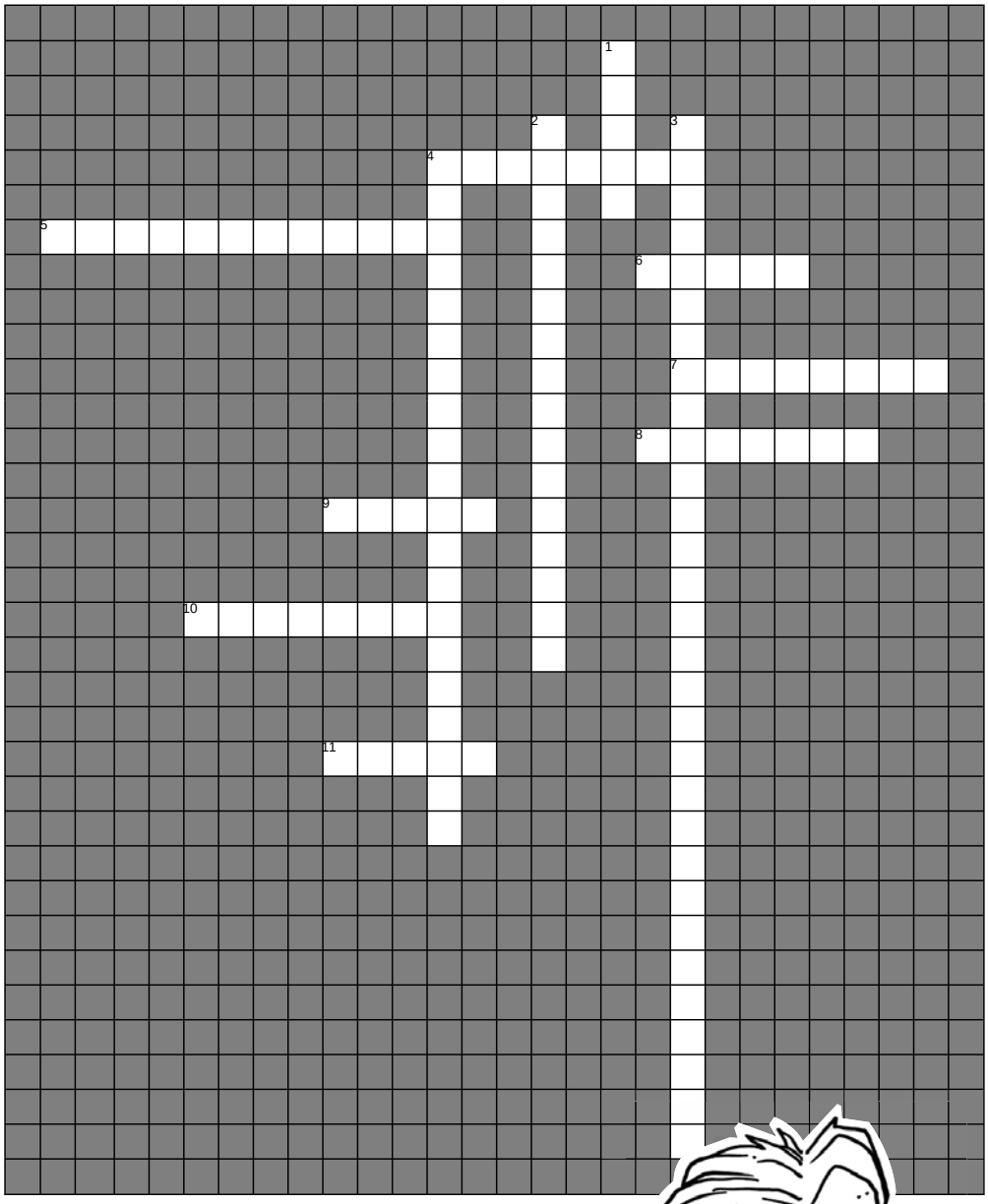
  Drug-drug interaction between repaglinide (PRANDIN), a short-acting insulin secretagogue, and gemfibrozil (Lopid) a lipid-lowering agent used to treat dyslipidemia. Sept, 2003

- **Orlaam (levomethadyl acetate hydrochloride)**

  Roxane Laboratories, Inc. is discontinuing the sale and distribution of ORLAAM. ORLAAM was removed from the European market in March 2001 following reports of severe cardiac-related adverse events, including QT interval prolongation, Torsades de Pointes and cardiac arrest. Sept 2, 2003

TOXICOLOGY CROSSWORD
CHEMICAL WEAPONS

Contributed by the Long Island Regional Poison and Drug Information Center



Down

1. A nerve agent developed by the Germans after WWI.
2. What was the name of the chemical that was placed in a can of vanilla soda to kill a 17 year male in Maryland on January 6, 2003?
3. What chemical caused refractory seizues to develop in a 15 month old Chinese girl after she ingested some of the powder that her parents had purchased to kill rodents in their kitchen?
4. What is the name of the enzyme that is blocked by the nerve agents?

Across

4. A drugs that can be used in the management of a severe Nerve agent poisoning
5. What chemical was added to heroin that caused over 300 addicts to show up in various emergency departments on the east coast with anticholinergic manifestations in 1995?
6. Another nerve agents that was developed by the Germans after WWI.
7. What substance was injected into Marzipan candy on Valentine's day a few years ago that caused the victims to lose their hair and have painful paresthesiaes in their hands and feet?
8. What was the name of the chemical used in the Nazi gas chambers in WWII?
9. On October 15,2003 what toxic chemical was identified in an envelope found at a mail processing center in Greensville, South Carolina?
10. In 1995 which toxic agent was released in the Tokyo subway system?
11. Another nerve agent developed by the Germans after WWI.

Answers: Down: *1. Sarin 2. Potassiumcyanide 3. Tetramethylenedisulfotetramine 4. Acetylcholinesterase* ***Across:*** *4. Atropine 5. Scolpolamine 6. Tabun 7. Thallium 8. Zyklon B 9. Ricin 10. Saringas 11. Soman*

State University of New York
Upstate Medical University

CNY Poison Center
750 East Adams Street
Syracuse, NY
13210

New York State Poison Centers
1-800-222-1222

July 2004

The NY State Poison Centers

TOXICOLOGY LETTER

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Toxicology Advice Centers • •

Administrative Phone Numbers - To obtain a consult in your area, call 1.800.222.1222.

Western New York Poison Center (WNY)
716.878.7871 • www.chob.edu/poison

Finger Lakes Regional Poison & Drug Info Center (FL)
585.273.4155 • www.FingerLakesPoison.org

Central New York Poison Center (CNY)
315.464.7078 • www.cnypoison.org

New York City Poison Control Center (NYC)
212.447.8152

Long Island Poison & Drug Info Center (LI)
516.663.4574 • www.LIRPDIC.org

Program Announcements • •

FL: The Finger Lakes Regional Poison Control Center has served the professional and the public since 1954. It was the first center to offer services to the public and the first center in New York State. It was also the first to offer services to the Deaf, WIC population and the Migrant Worker.

We are celebrating all year, but there will be the 50th Anniversary toxicology conference and grand celebration November 19-20, 2004. Speakers will include Michael McGuigan, Barry Rumack, Bill Robertson and John Trestrail.

Save the date.

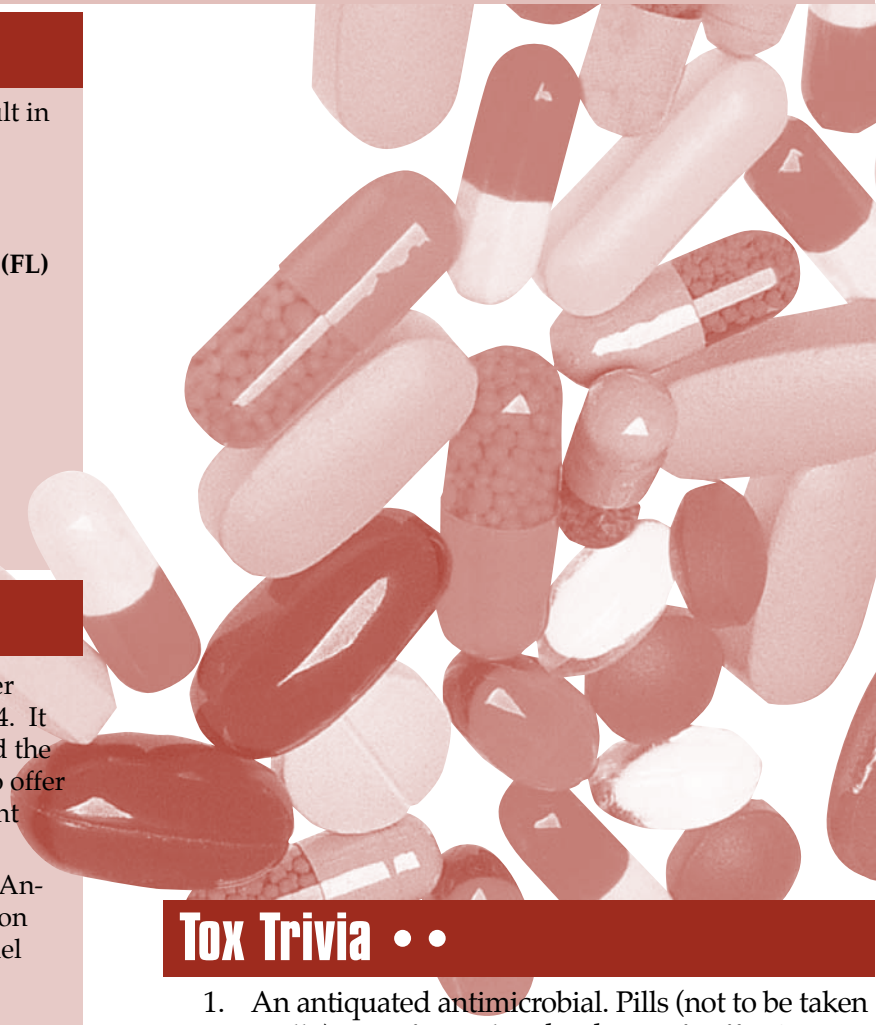
CNY: Case Conferences, Thursdays • 1:30-2:30pm

Please mark your calendars for the Eighth Annual Toxicology Teaching Day on November 3, 2004. More information to follow...

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

LI: *Critical Care Toxicology*, September 30, 2004 12-2PM by Dr Prashant Joshi.
The conference will be available by both TV or telephone for any health care professional that wants to participate.

Please call administrative telephone numbers for more information.



Tox Trivia • •

1. An antiquated antimicrobial. Pills (not to be taken orally) were formed in the shape of coffins?
2. Toxin causing opisthotonos, was used in the treatment of sedative overdose?
3. What was in the "universal antidote"?

NYPC Tidbits • •

Match the poison with the pest:

A. Honeybee	1. cantharidin
B. Poison Ivy	2. hyaluronidase
C. Blister beetle	3. urushiol
D. Fire ant	4. piperidine

Answers on page 6

FDA Safety Summaries April-June, 2004

Paradigm Quick-set Plus Insulin Administration Set

FDA and Medtronic, Inc. notified healthcare professionals of a Class I recall of Quick-set Plus infusion sets because of problems with bending of the infusion set's cannula or unintentional disconnection of the set at the insertion site that can interrupt insulin flow to diabetics who use them. These problems have resulted in a number of serious injuries, including some hospitalizations. May 20, 2004.

Children's Motrin Grape Chewable Tablets

FDA and McNeil alerted healthcare professionals that one manufacturing lot (Lot # JAM108, exp 1/06) of Children's Motrin (ibuprofen) Grape Chewable Tablets may mistakenly contain Tylenol 8-Hour extended release (acetaminophen) Geltabs. May 12, 2004

Desyrel (trazodone hydrochloride)

FDA and Bristol-Myers Squibb notified healthcare professionals of revisions to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections of the Desyrel labeling. In vitro drug metabolism studies suggest that there is a potential for drug interactions when trazodone is given with the CYP3A4 inhibitors ketoconazole, ritonavir, and indinavir.

Oxandrin (oxandrolone, USP)

Savient Pharmaceuticals, Inc. notified healthcare professionals of an important drug interaction between Oxandrin, a synthetic derivative of testosterone, and the oral anticoagulant warfarin for systemic anticoagulation. Concurrent dosing of Oxandrin and warfarin may result in unexpectedly large increases in the International Normalized Ratio (INR) or prothrombin time (PT).

Zelnorm (tegaserod maleate)

The FDA and Novartis notified healthcare professionals of an important drug warning and prescribing information for Zelnorm, a serotonin 5-HT_4 receptor partial agonist indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. This new information relates to a Warning for serious consequences of diarrhea and a Precaution for rare reports of ischemic colitis in post marketing use of Zelnorm. April 26, 2004

Cytotec Solutions, Inc. Products

FDA warned consumers not to purchase or consume products marketed as "street drug alternatives" by Cytotec Solutions, Inc., of Tampa, Fla. FDA analyses of products manufactured or distributed by Cytotec Solutions Inc., found the drugs diphenhydramine HCl, dextromethorphan, ephedrine, and the controlled substances GBL and GHB.

Abilify (aripiprazole), Seroquel (quetiapine fumarate), Clozaril (clozapine)

FDA notified healthcare professionals of revision to the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking these products. April 2004

Major Twice-A-Day 12 Hour Nasal Spray

Propharma, Inc., Miami, Florida issued a recall of Major Twice-A-Day 12 Hour Nasal Spray (Lot #K4496, Exp 10/06) because the lot was contaminated with Burkholderia cepacia bacteria. March 26, 2004

Zyprexa (olanzapine)

FDA and Lilly notified healthcare professionals of revision to the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking Zyprexa. FDA has asked all manufacturers of atypical antipsychotic medications, including Lilly, to add this Warning statement to labeling. March 2004

Public Health Advisory: Antidepressant Use in Children, Adolescents, and Adults

The FDA asked manufacturers of the following antidepressant drugs to include in their labeling a Warning statement that recommends close observation of adult and pediatric patients for worsening depression or the emergence of suicidality when treated with these agents. The drugs that are the focus of this new Warning are: Prozac (fluoxetine); Zoloft (sertraline); Paxil (paroxetine); Luvox (fluvoxamine); Celexa (citalopram); Lexapro (escitalopram); Wellbutrin (bupropion); Effexor (venlafaxine); Serzone (nefazodone); and Remeron (mirtazapine).
March 22, 2004

Calcium Channel Blocker Overdose and New Treatment Options

Case Report: *(Provided by the NYC Poison Control Center: Nicole Bouchard, MD, Fellow in Medical Toxicology)*

Jeanna M. Marraffa, Pharm.D. and Christine M. Stork, Pharm.D., DABAT

Central New York Regional Poison Center

A 10 month old male ingests one of his grandmother's Diltiazem CD® 300 mg. Approximately 5 hours later, he became obtunded and was noted by the family to have seizure like activity. Upon arrival to the Emergency Department (ED), the child was crying and hypotensive with a heart rate of 80 beats per minute. Initial blood glucose was 300 mg/dL. Intravenous calcium gluconate 20 mg/kg and glucagon 150 mcg/kg (total) was started without effect. Intravenous fluids, dopamine and epinephrine infusions were initiated also without desired effect.

What immediate interventions are required for this patient?

Despite significant advancements in supportive care, significant morbidity and mortality is associated with calcium channel blocker (CCB) and beta adrenergic antagonist (BAA) poisoning and all but trivial exposures should be treated as life-threatening. As with any life-threatening ingestion/exposure, attention to the ABC's (airway; breathing and circulation) is critical. This patient's airway was patent, however he had decreased breath sounds and mental status changes that do not allow him to protect his airway. Endotracheal intubation should be considered in these circumstances. Circulation is optimized through the use of various drugs aimed at increasing the amount of intracellular calcium. In patients presenting with altered mental status, an accurate assessment of glucose or empiric administration of glucose 1 g/kg is imperative. Thiamine should be considered, in conjunction with glucose, in any patient that may have thiamine deficiency (chronic alcoholism or malnourishment)

What is the differential diagnosis of toxin-induced hypotension and bradycardia?

Toxins that commonly cause bradycardia include: digoxin, organophosphates, beta receptor antagonists (BAA), non-dihydropyridine calcium channel blockers (diltiazem; verapamil) [CCB], presynaptic alpha$_2$ receptor agonists (clonidine; imidazoline derivatives), antidysrthymics and electrolyte abnormalities. Sedative hypnotics and opioids can also cause a small decrease in heart rate. Toxins that commonly cause hypotension include: beta receptor antagonists; non-dihydropyridine calcium channel blockers; dihydropyridine calcium channel blockers (nifedipine; amlodipine); alpha$_1$ receptor antagonists (prazosin; terazosin; phenothiazines); antidysrthymics; tricyclic antidepressants. Sedative hypnotics and opioids can cause a small decrease in blood pressure.

Once stabilized, is there any role for gastrointestinal decontamination?

Sustained-release products may be too large to fit up an orogastric tube. Some of the formulations of the sustained release products contain pellets that are designed for the extended/sustained release mechanism. If the formulation of the product is known, orogastric lavage may be beneficial in removing such internal components. CCB and BAA adhere well to activated charcoal; however, a large gastrointestinal burden may limit the usefulness of activated charcoal. (Example: 100 tablets of 240 mg verapamil SR will require 240 grams of activated charcoal to achieve a 10:1 charcoal to drug ratio). Whole bowel irrigation using polyethylene glycol electrolyte solution (Go-Lytley®) is advocated for patients with large ingestions of sustained release products with adequate bowel activity. The solution is given at 2 Liters/hour in adults (500 mL/hour in pediatric patients) through nasogastric administration until rectal effluent is clear, which typically takes approximately 4 to 6 hours. It may prevent toxicity in patients that would not otherwise manifest signs or symptoms of toxicity for 12-24 hours.

What is the typical course of CCB/BAA Poisoning?

CCB and BAA are available as regular release and sustained-release pharmaceutical formulations. Regular-release formulations induce signs and symptoms of toxicity within 1 to 2 hours after oral administration and almost immediately after intravenous dosing. Sustained-release formulations often have a delayed presentation of up to 12 to 24 hours after oral administration. The typical manifestations of toxicity include hypotension and bradycardia, which can proceed to cardiovascular collapse after life-threatening exposure. Atypical finding in CCB patients include the preservation of mental status even in patients with severe hypotention. This effects is not apparent after BBA exposure. Physical examination otherwise may reveal decreased bowel activity and laboratory examination may be significant for hyperglycemia after CCB poisoning. Insulin release from the beta islet cells of

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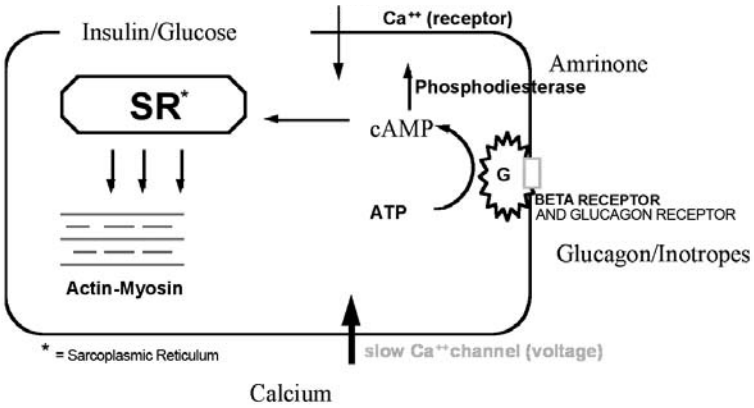
Calcium Channel Blocker Overdose...

Continued from page 3

the pancreas is dependent on calcium influx by a slow calcium channel. After CCB overdose, this slow calcium channel is antagonized resulting in impairment of insulin release. Laboratory examination in BAA poisoned patients may reveal hypoglycemia through a $beta_2$ mediated stimulation of insulin release. BAA also inhibits gluconeogenesis and glycogenolysis, which results in an impaired ability to recover from hypoglycemia.

What are the specific therapies for CCB/ BAA induced hypotension and bradycardia?



The beta receptor interacts with a G-protein to increase the function of adenylate cyclate in converting ATP to cAMP. cAMP increases cardiac contractility by increasing calcium release from the sarcoplasmic reticulum. cAMP is broken down by phosphodiesterase III. BAA inhibits the enzymatic production of cAMP. CCB antagonize the L-type (voltage sensitive) slow calcium channels to prevent the influx of calcium into myocardial and smooth muscle cells. This then inhibits calcium-triggered calcium release, which is the phenomenon of the release of calcium from the sarcoplasmic reticulum in response to calcium influx. This leads to a decrease in actin and myosin binding and a decrease in myocyte depolarization and contraction.

Specific therapy that may be considered in the treatment of hypotension and bradycardia caused by CCB and BAA includes:

Fluid:

Crystalloid fluids (eg: normal saline) increase intravascular volume. Crystalloid fluid administration should be administered first after toxin-induced hypotension. If a patient is hypotensive and has no evidence of heart failure, crystalloid fluid should be given as bolus administration of 20 mL/kg and may be repeated with consideration of the patient's fluid status and subsequent need for colloid preparations.

Atropine:

Atropine inhibits vagal nerve activity to increase heart rate. Atropine should be considered first in bradycardia thought to be caused by toxin associated depression of the SA and AV node. In the setting of CCB/BAA poisoning, there are many reported cases of the failure of atropine to increase the heart rate.

Calcium:

Calcium competes for slow calcium transport and is taken intracellularly through calcium channels that are not blocked in the presence of a CCB. Calcium is beneficial in both CCB and BAA toxicity by increasing available intracellular calcium. In the case of BAA toxicity, calcium should be instituted after glucagon administration. The dose of calcium chloride is 1 gram intravenously and up to 3 grams total. Calcium chloride can cause venous irritation. Therefore in patients with poor venous access (or children), calcium gluconate should be administered. The calcium ion equivalent dose is three times that of calcium chloride. Excessive dosing of calcium can lead to systemic hypercalcemia. To avoid this, serum calcium must be monitored if more than 3 or 4 grams of calcium chloride (9 to 12 grams of calcium gluconate) is administered in an adult.

Glucagon:

Glucagon increases production of cAMP and subsequent calcium release from the sarcoplasmic reticulum through a non-beta receptor mediated effect, as pictured in figure 1. Glucagon is efficacious in both CCB and BAA poisoned patients, however, it may be more effective in BAA toxicity as the normal pathway for cAMP production is antagonized (BAA). The adult dose of glucagon is a slow intravenous bolus of up to 10 mg (in divided doses) followed by a continuous infusion of the effective initial dose given each hour. Lower esophageal sphincter tone is decreased with glucagon, which may result in vomiting. Careful attention to airway management should be employed in patients with an altered mental status. Additionally, blood glucose levels should be monitored while on glucagon.

Insulin/Glucose:

High dose insulin with glucose to maintain euglycemia is shown to be beneficial in

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the treatment of CCB/BAA overdose. Animal models show that this treatment modality improves survival and human case series demonstrate an overall improvement in cardiac function and blood pressure. It is known that poisoning with CCB/BAA alters the normal metabolism of myocardial cells of fatty acids and forces them to become carbohydrate dependent. Additionally, CCBs inhibit calcium mediated insulin secretion from the beta islet cells of the pancreas and increase myocardial resistance to insulin. This therapy should be employed early in the course of toxicity due to the convincing, though limited data and the relative lack of serious side effects. The dose of insulin in adults should be initiated at 10 Units of regular insulin/hour that can be titrated to 1 Unit/kilogram/hour. Glucose therapy should be initiated to maintain serum glucose levels of > 100 mg/dl and serum glucose and potassium levels must be monitored closely throughout therapy.

Pacing:

Patients unresponsive to calcium, glucagon and insulin/glucose require aggressive care. Transcutaneous and transvenous pacing should be attempted; though there are cases of failure of pacing in the face of CCB/BAA poisoning.

Vasopressors:

Pharmacologic agents that increase and maintain perfusion may include dopamine, norepinephrine, epinephrine and dobutamine. Based on the clinical picture of toxicity, the institution of an agent with alpha$_1$ and beta$_1$ agonist properties (eg: norepinephrine, epinephrine) is the most reasonable option. To ensure adequate optimization of therapy, invasive hemodynamic monitoring with a pulmonary artery catheter may be warranted.

Phosphodiesterase Inhibitors:

Amrinone and milrinone inhibit the breakdown of cAMP through phosphodiesterase III inhibition. These agents cause peripheral vasodilation and should only be instituted in the presence of vasopressors.

Intraaortic balloon pump/ Cardiopulmonary Bypass/ Extracorporeal Membrane Oxygenation (ECMO):

Intraaortic balloon pump is used with success when other agents have failed. An intraaortic balloon pump is inserted to provide mechanical circulatory assistance to the failing heart. For placement, a patient must have adequate blood pressure, so it should be considered early on in the refractory patient. Cardiopulmonary bypass and ECMO have been used, with variable success, in the CCB/BAA poisoned patient.

Are there any concerns with calcium administration in the patient with toxin-induced bradycardia?

In any patient with bradycardia and unknown etiology, the presence of digoxin should be considered and excluded prior to the administration of calcium. In animal models and in human case reports, the administration of calcium worsened the cardiotoxicity associated with digoxin and resulted in the phenomenon of 'stone heart' and death. Transvenous pacing in the digoxin poisoned patient has been associated with ventricular dysrhythmias secondary to increased ventricular irritability. Digoxin toxicity should be ruled out in any patient with toxin induced bradycardia and treatment with digoxin specific Fab fragments should be employed prior to calcium and pacing.

Are there any investigational/theoretical therapies available in the treatment of CCB/BAA poisoning?

Vasopressin is recently implicated in having positive results and outcomes in asystolic cardiac arrest, ventricular fibrillation and ventricular tachycardia. Additionally, it is proposed to be an effective adjunct to vasopressor therapy in vasodilatory shock. The proposed mechanism for which vasopressin exerts its vasoconstrictive properties is through V_1 receptor agonism. The V_1 recptor, when activated increases myocyte depolarization by increasing intracellular calcium and ultimately causes vasoconstriction. In addition to its affects on V_1 receptor, vasopressin causes vasoconstriction through inhibition of K-ATP sensitive channels. These channels normally open to cause vasodilation through an extracellular shift of potassium. Though limited, vasopressin appears to have a positive increase on SVR and improve hypotension. Data related to vasopressin's effect on toxin-induced hypotension is not available, however, it

Continued on page 6

Calcium Channel Blocker Overdose...

Continued from page 5

is a reasonable agent to institute in refractory CCB/BAA poisoned patients.

4-aminopyridine increases the calcium influx by blocking voltage sensitive potassium channels. It also directly increases skeletal and cardiac muscle contractility. 4-aminopyridine has a narrow therapeutic index with its major toxicity being seizures, which has limited its use.

Digoxin has also been used experimentally in CCB poisoning. Cardiac glycosides, including digoxin, inhibit the sodium-potassium-ATPase pump and thereby increase intracellular calcium. However, due to the lack of safety and efficacy data in this setting, further research must be employed before digoxin should be administered to CCB/BAA poisoned patients

Are all CCB's the same?

There are three classes of calcium channel blockers: the phenylalkylamines (eg: verapamil); the benzothiazines (eg: diltiazem) and the dihydropyridines (eg: nifedipine, amlodipine). All three classes affect the slow (L-type) voltage-gated calcium channels however; each class has different affinities for the channel, which produces different degrees of peripheral vasodilation and SA and AV nodal depression. Verapamil has the most profound inhibitory effects on the SA and AV node whereas, therapeutic doses of diltiazem has only moderate conduction effects. However, in overdose, AV and SA node depression is expected to be profound secondary to verapamil and diltiazem. Contrasted to this, dihydropyridines have little affinity for the myocardial calcium channels but have the greatest effect on peripheral vascular smooth muscle. Dihydropyridine toxicity generally manifests as hypotension with a reflex tachycardia secondary to their pharmacologic properties.

Are all BAA's the same?

Beta-receptor antagonists competitively antagonize the effect of catecholamines at cardiac and peripheral beta-receptors. Some BAA are specific for $beta_1$ receptors, however; in overdose, receptor selectivity is lost. In addition to differences in receptor specificity, some BAA are lipophilic, cross the blood brain barrier and result in sedation and even seizures. Seizures after BAA toxicity should first be managed with benzodiazepines and barbiturates, if necessary. Other BAA possess a 'membrane stabilizing effect' which causes fast sodium channel blockade and manifest with QRS complex widening on the electrocardiogram. BAA with 'intrinsic sympathomimetic activity' act as partial agonists at beta receptors and may be protective in overdose.

Case Conclusion

The child was intubated for respiratory support. Activated charcoal by nasogastric tube administration was given followed by whole bowel irrigation at 500 ml/hour. Insulin therapy was started at 1 Unit/kilogram/hour with 1 g/kilogram/hour of glucose to maintain blood glucose levels greater than 100 mg/dL. Despite aggressive supportive care, the child continued to deteriorate clinically. He received multiple doses of atropine for profound bradycardia and required aggressive CPR measures. The child experienced an asystolic arrest and expired approximately 13 hours after the ingestion.

Conclusion

CCB and BAA exposures continue to result in numerous deaths from poisoning annually. Toxicity includes bradydysrhythmias and hypotension, which are extensions of their pharmacologic effects. Because of the lethality of such agents, aggressive measures must be attempted for gastrointestinal decontamination as well as in the management of symptomatic patients.

References

1. *Dunser MW, Wenzel V et al. Management of Vasodilatory Shock: Defining the Role of Arginine Vasopressin. Drugs 2003; 63(3): 237-256*
2. *Holstege CP, Hunter Y et al. Massive Caffeine Overdose Requiring Vasopressin Infusion and Hemodialysis. J Toxicol Clin Toxicol 2003; 41(7): 1003-1007.*
3. *Salhanick SD, Shannon MW. Management of Calcium Channel Antagonist Overdose. Drug Safety 2003; 26(2): 65-79.*
4. *Reith DM, Dawson AH et al. Relative Toxicity of Beta Blockers in Overdose. J Toxicol Clin Toxicol 1996; 34(3): 273-278.*
5. *Yuan TH, Kerns WP et al. Insulin-Glucose as Adjunctive Therapy for Severe Calcium Channel Antagonist Poisoning. J Toxicol Clin Toxicol 1999; 37(4): 463-474.*
6. *Brubacher JR. (2002). Beta Adrenergic Antagonists. In Goldfrank LR, Flomenbaum NE, Lewin NA et al., Goldfrank's Toxicologic Emergencies 7th edition, (741-761), McGraw-Hill Medical Publishing Division: New York*
7. *DeRoos F. (2002). Calcium Channel Blockers. In Goldfrank LR, Flomenbaum NE, Lewin NA et al., Goldfrank's Toxicologic Emergencies 7th edition, (762-774), McGraw-Hill Medical Publishing Division: New York*

Tox Trivia Answers • •

1. mercuric chloride
2. strychnine
3. magnesium oxide, tannic acid and activated charcoal

NYPC Tidbits Answers • •

A. 2

B. 3

C. 1

D. 4

SPI CORNER TOPIC:
YOHIMBE

Contributed by: Joe Tschopp, RN, SPI, Central New York Regional Poison Center, Syracuse, NY

Yohimbe is found in many over the counter erectile dysfunction and sports enhancement supplements. Some common product names that contain yohimbe include Corynanthe yohimbe, Rubaceae and Rauwolfia Serpentina. Common brand names include Actibine, Aphrodyne, Enzyte, and Mederek.

The active alkaloid component derived from Yomhimbe is Yomhimbine. Yohimbine is a potent central and peripheral alpha-adrenergic type 2 adrenoreceptor antagonist. Toxic effects seen are as a result of decreases in central feedback inhibition causing increased release of norepinephrine.

Yohimbine is increasing in popularity largely due to its tumescent effect. In the vascular system, however, effects are as a result of increased norepinephrine. Patients may experience significant tachycardia and hypertension. End organ manifestations are as a result of shearing forces on vessel walls and can include central nervous system and cardiac manifestations. Additional effects that have been reported after ingestion include tremors, hyperinsulinemia, and hallucinations.

Treatment of patients after yohimbine ingestion is largely supportive. Patients should have careful attention to basic management with evaluation of other potential ingestants. Patients with central nervous system manifestations along with hypertension and tachycardia may benefit from benzodiazepines. Hypertension should be managed aggressively to mitigate potential end organ toxicity. Judicious use of nitroprusside is generally effective and desirable due to ease of titration.

Select References:

Betz, JM, White KD: Gas chromatographic determination of yohimbine in commercial yohimbine products. J AOAC Int. 1995; 78:1189-1194

Goldberg MR Robertson D: Yohimbine: a pharmacological probe for study of the alpha 2-adrenoceptor. Pharmacol Rev 1983;35:143-180

TOXICOLOGY CROSSWORD
POISONOUS PLANTS

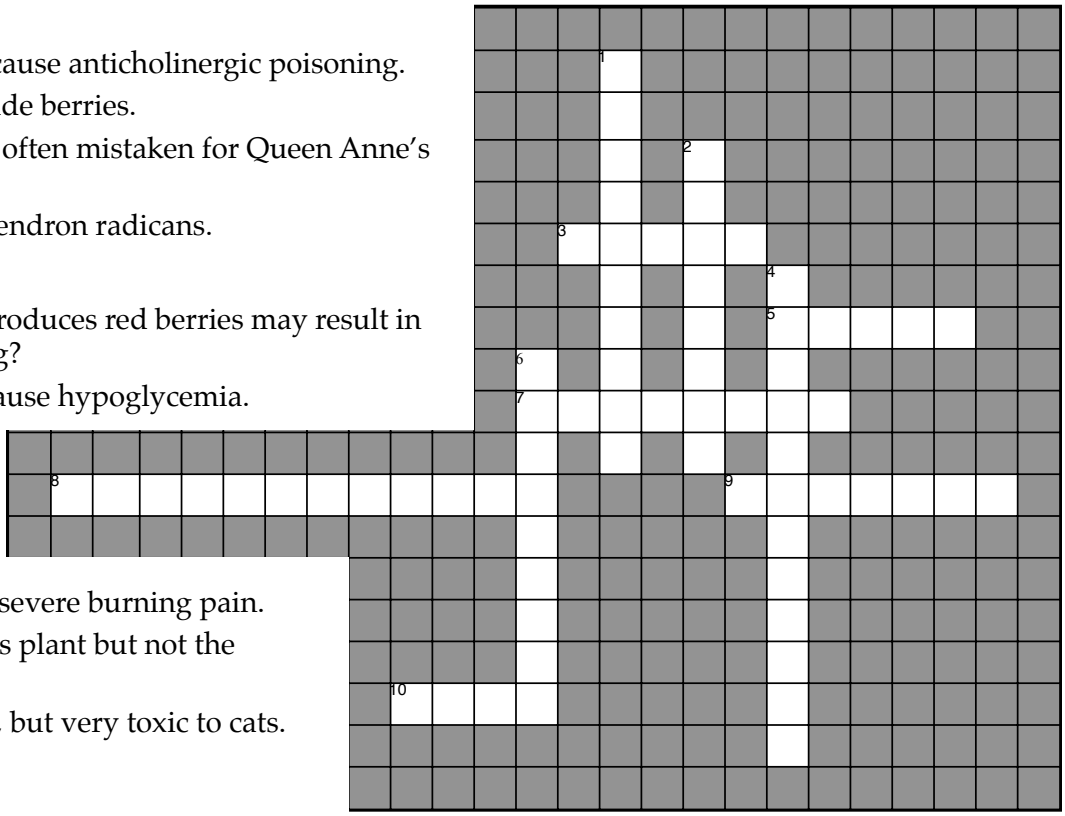
Contributed by Linda Jutton, RN, CSPI & Mary Halsey-Claps, RN, CSPI - CNY Poison Center

Down

1. Ingestion of this plant can cause anticholinergic poisoning.
2. Toxic substance in nightshade berries.
4. Which highly toxic plant is often mistaken for Queen Anne's Lace or Wild Carrot?
6. Common name for toxicodendron radicans.

Across

3. Which holiday plant that produces red berries may result in severe nausea and vomiting?
5. Eating this fruit raw may cause hypoglycemia.
7. Which plant causes toxicity similar to that of digoxin?
8. A common exposure in many kitchens resulting in severe burning pain.
9. You can eat the stalks of this plant but not the leaves.
10. Non-toxic plant to humans, but very toxic to cats.



Answers: Down: *1. Jimsonweed 2. Solanine 4. Waterhemlock 6. Poison Ivy* ***Across:*** *3. Holly 5. Ackee 7. Oleander 8. Chili Peppers 9. Rhubarb 10. Lily*

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Upstate Medical University

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New York State Poison Centers
1-800-222-1222

October 2004

The NY State Poison Centers

TOXICOLOGY LETTER

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Toxicology Advice Centers • •

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New York City Poison Control Center (NYC)
212.447.8152

Long Island Poison & Drug Info Center (LI)
516.663.4574 • www.LIRPDIC.org

Program Announcements • •

FL: The Finger Lakes Regional Poison Control Center has served the professional and the public since 1954. It was the first center to offer services to the public and the first center in New York State. It was also the first to offer services to the Deaf, WIC population and the Migrant Worker.

We are celebrating all year, but there will be the 50th Anniversary toxicology conference and grand celebration November 19-20, 2004. Speakers will include Michael McGuigan, Barry Rumack, Bill Robertson and John Trestrail.

Save the date.

CNY: Case Conferences, Thursdays • 1:30-2:30pm

Please mark your calendars for the Eighth Annual Toxicology Teaching Day on November 3, 2004. Please call 315-464-7078 for a brochure.

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

LI: *Toxicology of Coma,* 9/30/04, 12:00 PM - 2:00 PM
Critical Care Toxicology, 10/26/04, 12:00 PM - 2:00 PM
Toxicology and Pregnancy, 11/30/04, 12:00 PM - 2:00 PM

Please call administrative telephone numbers for more information.

Tox Trivia • •

1. The Marsh test may be used to determine the presence of this toxin.
2. What toxic substance was found in samples of Beethoven's hair?
3. What Thanksgiving table scrap can cause pancreatitis to your dog?

NYPC Tidbits • •

1. Readily available treatment will reduce the half-life of theophylline.
2. Naloxone can be effective in this non-opioid poisoning.
3. Withdrawal symptoms may occur soon after and be prolonged after exposure to this drug of abuse.

Answers on page 6

FDA Safety Summaries July-September, 2004

Geodon (ziprasidone)

FDA and Pfizer notified healthcare professionals of revision to the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking Geodon. FDA has asked all manufacturers of atypical antipsychotic medications, including Pfizer, to add this Warning statement to labeling. *August 2004*

Remicade (infliximab)

FDA and Centocor revised the WARNINGS and ADVERSE REACTIONS sections of the labeling for Remicade, indicated for the treatment of rheumatoid arthritis and Crohn's disease. Cases of leukopenia, neutropenia and pancytopenia, some with fatal outcome, and cases of CNS manifestation of systemic vasculitis, were described in patients receiving Remicade. The ADVERSE REACTIONS section was updated to include neutropenia, pericardial effusion and systemic and cutaneous vasculitis. *August 11, 2004*

Lovenox (enoxaparin sodium injection)

FDA and Aventis Pharmaceuticals revised the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of labeling, describing the need for a dosage adjustment for patients with severe renal impairment (creatinine clearance <30mL/min) who have increased exposure to enoxaparin. No specific dosage adjustment is required in patients with mild or moderate renal impairment or in low-weight patients. However, low-weight patients should be observed carefully for signs and symptoms of bleeding. *July 2004*

Avastin (bevacizumab)

FDA and Genentech, Inc. issued an important drug warning to healthcare providers that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to Avastin. The risk of fatal arterial thrombotic events is also increased. In randomized, active-controlled studies conducted in patients with metastatic colorectal cancer, the risks of a serious arterial thrombotic event was approximately two-fold higher in patients receiving infusional 5-FU based chemotherapy plus Avastin, with an estimated overall rate of up to 5%. A revised Avastin package insert containing more detailed information on arterial thromboembolic events is in development. The current Avastin package insert is provided below. *August 12, 2004*

Risperdal (risperidone)

FDA and Janssen revised the WARNINGS section of labeling, describing the increased risk of hyperglycemia and diabetes in patients taking Risperdal. *July 2004*

Effexor (venlafaxine HCl)
Effexor XR (venlafaxine HCl)

FDA and Wyeth Pharmaceuticals notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of labeling to alert healthcare providers of two important safety issues. Neonates exposed to Effexor, other SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester of pregnancy have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Also, patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The warning recommends patients being treated with antidepressants be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases. *June 3, 2004*

Serzone (nefazodone hydrochloride) Tablets

FDA and Bristol-Myers Squibb notified healthcare professionals of revisions to the INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, and WARNINGS sections to encourage healthcare providers to engage in a thorough risk-benefit analysis, including consideration of the risk of hepatic failure associated with Serzone treatment, when deciding among alternative treatments available for depression. In addition, healthcare providers and consumers are cautioned about the need for close observation of patients being treated with antidepressants for clinical worsening of the symptoms of depression, for the emergence of suicidality, and for the emergence of a variety of other symptoms that may represent a worsening of the patient's condition. *June 18, 2004*

Wellbutrin (bupropion hydrochloride) Tablets
Wellbutrin SR (bupropion hydrochloride) Sustained-Release Tablets
Wellbutrin XL (bupropion hydrochloride) Extended-Release Tablets

FDA and GlaxoSmithKline notified healthcare professionals of revisions to the WARNINGS and PRECAUTIONS sections of labeling to alert healthcare professionals that patients with major depressive

Continued on page 5

A Life-Threatening Ingestion

Case Report:

By: Davis Clark DO, Christine Stork PharmD, DABAT. Central New York Poison Center and Department of Emergency Medicine, Upstate Medical University

MJ is a 42 year old male who presents to the Emergency Department a maximum of 2 hours after allegedly ingesting the contents of several empty pill bottles. Prescription containers found included Toprol XL®, Metformin, Benzonatate, Isosorbide dinitrate, Quinine Sulfate, Digoxin® and Colchicine (90 tablets missing, 0.6mg/tab). MJ is awake and alert, but somewhat confused. Initial physical examination and vital signs are unremarkable.

What are the initial measures are appropriate in the care of MJ?

Any patient presenting for emergency care should be ensured adequate airway, breathing and circulation. MJ is talking, his breath sounds are equal and bilateral and he has good pulses in all four extremities, which indicates maintenance of these functions. Due to altered mental status, evaluation for hypoglycemia is appropriate as is empiric administration of glucose 1 g/kg intravenously. In fact, there are several toxicologic scenarios where bedside glucose testing may lead to underestimation of cerebral hypoglycemia as a cause of alteration in mental status. Examples include aspirin where central nervous system hypoglycemia can cohabitate with euglycemia in the periphery and acetaminophen where publications indicate that acetaminophen levels of 300 mg/L can falsely elevate the fingerstick glucose reading by as much as 80 mg/dL.

All patients intentionally attempting to harm themselves using drug exposure should be evaluated for common life-threatening ingestions where early evaluation may lead to improvement in patient outcome. The patient should receive a 12 lead ECG as indicated by the historical ingestants and for potential exposure to tricyclic antidepressants. A QRS complex duration of greater than 100 msec is considered clinically relevant. In addition, an acetaminophen level is used to provide an indication of risk as well as a guideline for management following potential exposure. As many as 1 in 500 patients require treatment with the antidote without providing a history of exposure to acetaminophen. In this patient, a digoxin level will also provide significant information.

Are any of the historical medications of concern in this patient?

Benzonatate, Isosorbide dinitrate, or Metformin are not expected to result in severe, life threatening toxicity in this patient. However, many of the historical agents are well known to result in potentially life-threatening effects:

- Toprol XL® (metoprolol) is a beta blocker. Expected findings after exposure include bradycardia, impaired cardiac contractility and hypotension. At this time, the patient should be monitored for the development of hypotension and bradycardia.
- Quinine Sulfate is an antimalarial agent that is touted effective for the treatment of leg cramps. Quinine inhibits sodium and potassium channels. Inhibition of the fast sodium channel (phase 0) causes negative cardiac inotropy, slowed depolarization, and results in prolonged QRS complex duration. Potassium channel inhibition causes repolarization delays, thereby resulting in prolongation of the QT interval which may predispose the patient to ventricular dysrythmias (Torsades de Pointes). Retinal toxicity is also reported and manifests as blurry vision, visual field constriction and double vision. Lastly, "Cinchonism" may occur resulting in the classic findings of nausea, vomiting, decreased hearing, tinnitus and headache. This patient should be monitored for ECG abnormalities at this time.
- Digoxin overdose results in excessive inhibition of Na-K ATPase which inhibits potassium/sodium exchange and ultimately results in excessive intracellular calcium. In addition, digoxin increases automaticity of non-pacemaker cells while decreasing AV nodal conduction. Acute digoxin toxicity typically manifests in nausea, lethargy, confusion, weakness and hyperkalemia. Potassium levels exceeding 5 mEq/L after acute overdose are predictive of poor outcome. This patient should be monitored for ECG manifestations of toxicity, digoxin levels and hyperkalemia.
- Colchicine is the medicine most feared in this particular ingestion. European data indicates that ingestions of more than 0.8mg/kg result in fatality and ingestions of 0.5-0.8 mg/kg are potentially fatal. According to the latest report of

Continued on page 4

Continued from page 3

data from the American Association of Poison Control Center's Toxic Exposure Surveillance System, there were 139 reports of exposure to colchicine treated in a health care facility, 5 resulting in death. Colchicine acts through inhibition of mitosis during metaphase of dividing cells. This is achieved through binding to the intracellular protein tubulin, preventing its alpha and beta forms from polymerizing to form microtubules. These effects occur in all cell lines of the body and explain both the therapeutic effects and the multi organ toxicity seen after poisoning (See Figure). Although all cell lines are affected, rapidly diving cells are affected first as gastrointestinal irritation. Later, patients may succumb due to asystolic cardiac arrest (day 2-5). Late causes of death are due to severe bone marrow depression. MJ has an estimated ingestion of 0.9 mg/kg of colchicine.

Is Poisoning associated with therapeutic use of colchicines?

The dosing guidelines for the use of colchicine after acute gout do not include limits in dosing after therapeutic failure. The current guidelines state that after acute gouty episodes a dose of 1-1.2 mg orally should be followed by 0.5-0.6 mg hourly until the pain is relieved or nausea, vomiting or diarrhea occur. These are the very symptoms identified as the early manifestations of life-threatening toxicity. If this dose is administered intravenously, such initial warning signs may be absent because gastrointestinal cells are not directly exposed to the toxin. In some case reports, both oral and intravenous colchicine were administered concurrently, the error resulting in fatality.

What other toxins have similar effects to colchicine?

Colchicine is extracted for the autumn crocus, *Colchicum autumnale*. Podophyllum is also a natural product obtained as an extract of the mayapple. The extracted resin from the roots and dried rhizomes are used to treat warts, specifically condyloma accuminatum. Much like colchicine, podophyllum inhibits mitotic spindles during metaphase of the cell cycle.

What other interventions are now appropriate after consideration of colchicine toxicity?

Gastrointestional decontamination should be aggressive in an attempt to remove the small amount of colchicine that would be required to enhance patient outcome. MJ presents a maximum of 2 hours after exposure. Initial therapy should include gastric lavage with activated charcoal. Gastric lavage should be initiated using the largest tube possible (40F in an adult). The patient should be placed in the left lateral decubitus position if possible to minimize drug passage through the pylorus. In this case, even small amounts of drug passage may result in lethality. Therefore, 1 g/kg of activated charcoal should be administered prior to the initiation of gastric lavage. It is important to note that gastric emptying procedures such as gastric lavage and syrup of ipecac are not demonstrated to improve outcome in the majority of overdose patients. In all studies to date, the sickest patients were excluded and subgroup analysis was not performed to detect select subgroups where gastric emptying may be beneficial. Due to the lethal nature of this overdose history, aggressive therapy is warranted. Following gastric emptying, activated charcoal 1 g/kg should again be administered in an attempt to bind residual toxin.

Therapy for metoprolol and quinine will be initiated based upon the development of above stated toxic effects. A digoxin level and potassium concentration will quickly substantiate or rule out toxicity due to digoxin.

The potential for colchicine toxicity should be managed expectantly with careful observation. Early morbidity within the first 2-5 days can be expected due to asystolic cardiac arrest. Patients should be placed in a monitored setting and high-risk patients should be evaluated for prophylactic placement of a cardiac pacer. Patients surviving the early phase should be monitored for bone marrow suppression. Typically, patients who go on to develop significant bone marrow depression will exhibit a leucocytosis in the early phase. These patients may benefit from Growth Colony Stimulating Factor (GCSF). Finally, FAB fragments may be available in the future and hold promise after their successful use in France.

Emergency Department course

MJ was sedated, paralyzed and then intubated to protect his airway. He received activated charcoal, orogastric lavage, and a subsequent dose of activated charcoal. The patient remained sedated and intubated during the initial monitoring period. An initial digoxin level returned at 3.9 ng/mL. A repeat level 4 hours later was 1 ng/mL, ECG monitoring revealed no abnormalities. After 48 hours the patient was extubated and the patient was discharged from psychiatry clinically normal 7 days after exposure. White blood cell count was 7.2 on the day of admission, peaked at 14 on day 2 and returned to the 7 range thereafter with 5 days of follow-up measurements available.

Continued on page 5

FDA Safety Summaries

Continued from page 2

disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The warning recommends patients being treated with antidepressants be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases. May, 2004.

Paxil (paroxetine hydrochloride) Tablets
Paxil CR (paroxetine hydrochloride) Controlled-Release Tablets

FDA and GlaxoSmithKline notified healthcare professionals of revisions to the WARNINGS and PRECAUTIONS sections of labeling to alert healthcare professionals that patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications. The warning recommends patients being treated with antidepressants be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases. *May 2004*

Domperidone

FDA warned healthcare professionals and breastfeeding women not to use an unapproved drug, domperidone, to increase milk production (lactation). The agency is concerned with the potential public health risks associated with domperidone. FDA took these actions because it has become aware that some women are purchasing this drug from compounding pharmacies and from foreign sources. Although domperidone is approved in several countries outside the U.S. to treat certain gastric disorders, it is not approved in any country, including the U.S., for enhancing breast milk production in lactating women and is also not approved in the U.S. for any indication. June 10, 2004

Crestor (rosuvastatin)

FDA issued a Public Health Advisory notifying healthcare professionals of a revised package insert for use in the 22 member states of the European Union (EU). The changes to the European labeling are in response to adverse event reports in patients receiving Crestor and highlight certain patient populations who may be at an increased risk for serious muscle toxicity (myopathy) associated with Crestor use, especially at the highest approved dose of 40 mg. These risk factors and many of the recommendations for how to minimize the risk of myopathy are already captured in the FDA approved labeling for Crestor in the U.S. FDA alerted physicians to carefully read the Crestor product label and follow the recommendations for starting doses, dose adjustments, and maximum daily doses to minimize the risk of myopathy in individual patients. *June 09, 2004*

A Life-Threatening Ingestion

Continued from page 4

Select References.

Bismuth C, Baud F, Dally S. Standardized prognosis evaluation in acute toxicology its benefit in colchicines, paraquat and digitalis poisonings. *Journal de Toxicologie Clinique et Experimentale 1986, T. 6, N 1-33—38.*

Folpini A, Furori P. Colchicine toxicity – clinical features and treatment. Massive overdose case report. *J Toxicol Clin Toxicol 1995;33:71-77.*

Litovitz et al. 2002 Annual report of the American association of poison control centers toxic exposure surveillance system. *Am J Emerg Med 2003;21(5):353421.*

McCann B, Hunter R. Late diagnosis of severe colchicines intoxication. *Pediatrics 2002;109:971-973.*

McIntyre IM, Ruszkiewicz AR, Crump K, Drummer OH. Death following colchicines poisoning. *J Forensic Sci 1994;39:280-286.*

Tox Trivia Answers • •

1. arsenic
2. lead
3. Turkey skin

NYPC Tidbits Answers • •

1. multiple doses of activated charcoal
2. clonidine
3. GHB (gamma hydroxy butyrate)

SPI CORNER TOPIC:

ARE YOU READY FOR AN ETHYLENE GLYCOL INGESTION?

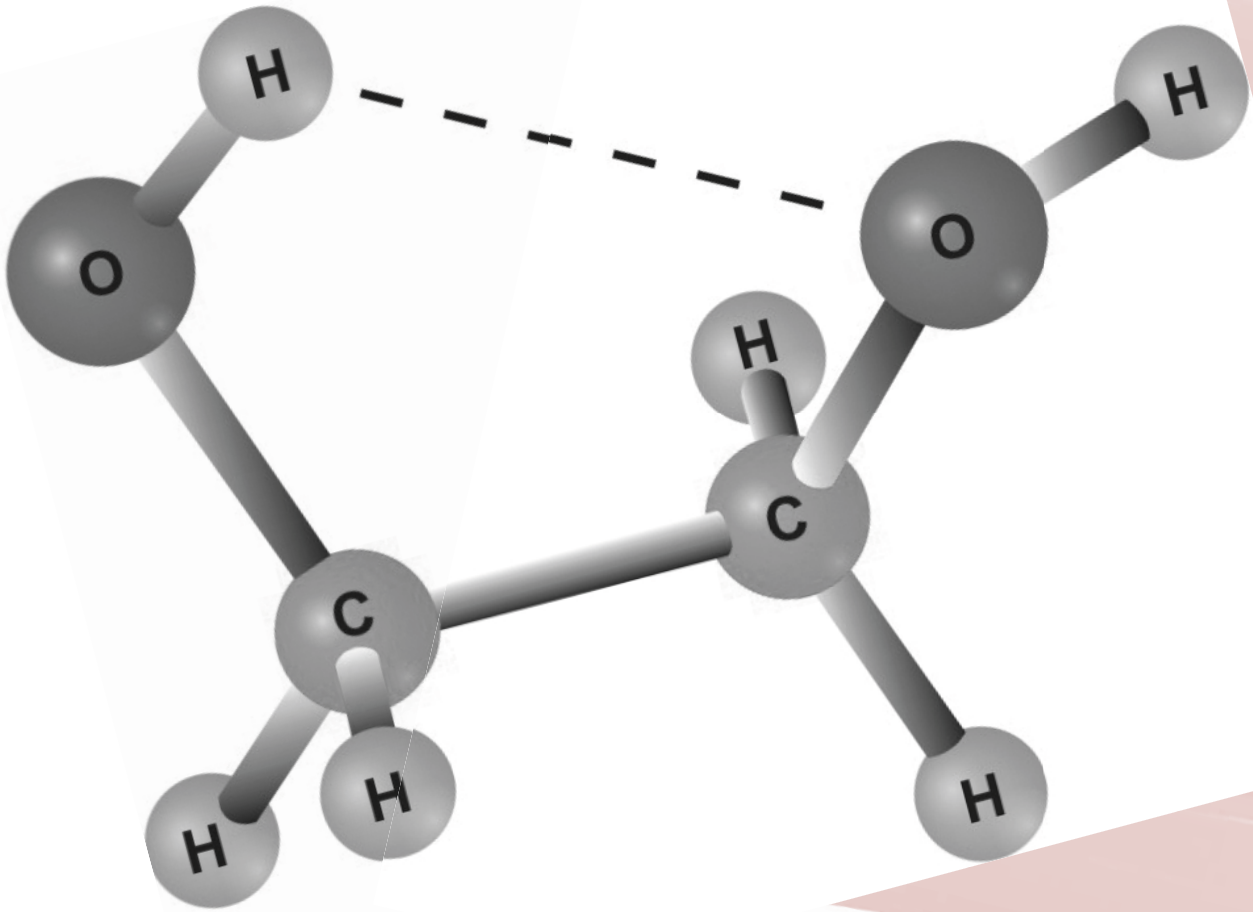
Contributed by: Laurie McGraw, RN, CSPI, Deborah Anguish, RN, CSPI, Central New York Poison Center, Syracuse, NY

Ethylene glycol is used in a wide variety of products. Most exposures occur as a result of the ingestion of automobile antifreeze. Accidental ingestions occurring in children may be a result of improper storage in a container that looks appealing to drink.

Ethylene glycol is slowly metabolized over several hours to an organic acid. Symptoms result from effects of the parent alcohol and more specifically from the metabolites. Early on, patients can be asymptomatic, even after life-threatening exposure, or can appear inebriated similar to after ingesting ethanol. Ethylene glycol is metabolized into glycolic, glyoxalic and oxalic acids. Late presenting patient will present with a progressive anion gap metabolic acidosis which can be severe. Clinical manifestations most commonly seen in this stage include altered mental status and high respiratory rate. Other symptoms may include: QT prolongation, cardiac dysrhythmias and renal tubular necrosis.

Treatment:

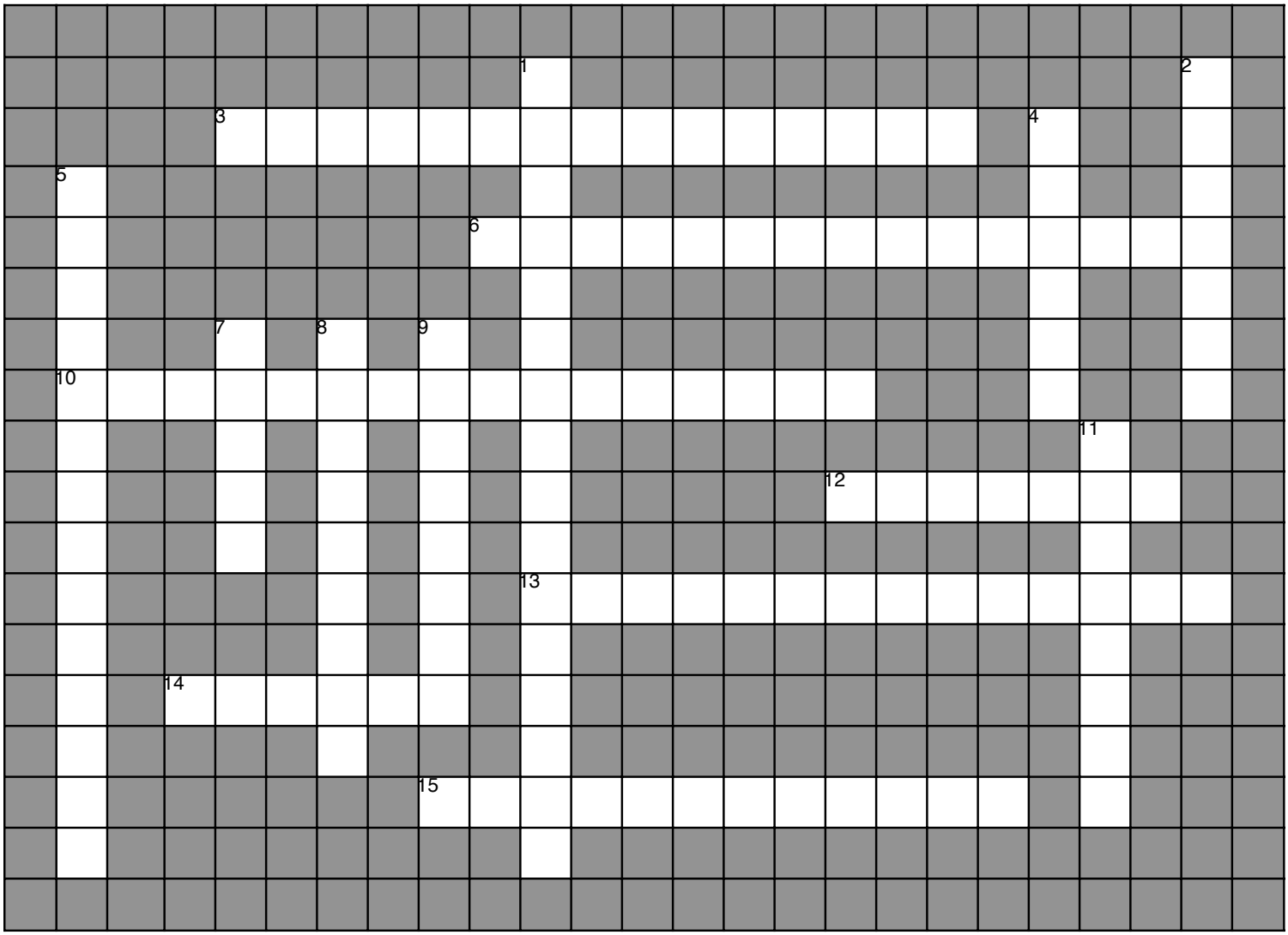
Ethylene glycol levels are considered an emergent blood test; know where your facility sends levels or call us for guidance. Obtaining results may take several hours. Ethylene glycol levels can be estimated using calculation of amount ingested and percentage of the product. However this is never exact. First and foremost assess the patient. Remember ABC's, may need to consider giving glucose in patients with altered mental status. Obtain baseline electrolytes, consider ABG's, and an ethanol level, elevated ethanol levels. Also consider getting an osmol gap, A large gap can be helpful, whereas a small gap does not exclude toxicity. If there is a potential for significant ethylene glycol poisoning, blocking metabolism using fomepizole (Antizol®) or ethanol is indicated. Hemodialysis should be used in cases where there is a significant amount of ethylene glycol parent toxin available and also in cases where acidosis has developed. Other ancillary treatments include include thiamine and pyridoxine. Remember, education is always the key to prevention.



TOXICOLOGY CROSSWORD

COLORS AND ODORS

Contributed by Laurie Piwinski, RN, CSPI



Across

3. Smells like rotten eggs
6. Colors the stool red
10. Smell like garlic
12. Also smells like garlic
13. Smells like pears
14. Emesis is blue-green in color
15. Smells like carrot

Down

1. Smells like wintergreen
2. Smells like bitter almond
4. Causes a silver coloration to the skin
5. Odorless, colorless gas
7. Smells like peanuts
8. Blue green emesis and lobster red skin
9. Smells like freshly mown hay
11. Creates an orange tinge to urine

Answers: Across: 3. Hydrogensulfide, 6. Phenolphthalein, 10. Organophosphates, 12. Arsenic, 13. Chloralhydrate, 14. Iodine, 15. Waterhemlock, Down: 1. Methylsalicylate, 2. Cyanide, 4. Silver, 5. Carbonmonoxide, 7. Vacor, 8. Boricacid, 9. Phosgene, 11. Rifampin

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New York City Poison Control Center (NYC)
212.447.8152

Long Island Poison & Drug Info Center (LI)
516.663.4574 • www.LIRPDIC.org

Program Announcements • •

FL: Monthly conference: every 4 weeks on Thursdays starting Jan 27th (11 am to noon), and every 4 weeks on Tuesdays starting Feb 1st, 2005 (10 am-11 am).

CNY: Please mark your calendars for our Nineth Annual Toxicology Teaching Day to be held in the Fall of 2005. More information to come.

NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

LI: January 27, 2005: Pediatric Toxicology
Howard Mofenson, MD

March 3, 2005: Herbal Toxicology
Ms. Elaine Yum, RPH,CSPI

March 30, 2005: Sports Toxicology
David Lee, MD

These conferences are available by telephone and broadband TV format from 12-2PM

Contact Tom Caraccio at *Tcaracci@winthrop.org* to register

Please call administrative telephone numbers for more information.

Tox Trivia • •

1. Anesthetic removed from the market in 1976 because of studies linking it to cancer in animals?
2. The presence of toxins in neonatal hair indicates an exposure in what trimester of pregnancy?
3. The only method of testing for anabolic steroid use accepted by the International Olympic Committee?

NYPC Tidbits • •

1. What is a common over the counter medication that can cause a false positive for PCP in a urine drug screen?
2. Toxic alcohol metabolized to formic acid?
3. Dermal post mortem finding after CO exposure?

Answers on page 6

FDA Safety Summaries September–December 2004

Bicillin C-R (penicillin G benzathine and penicillin G procaine injectable suspension)

Bicillin L-A (penicillin G benzathine injectable suspension)

King Pharmaceuticals and FDA reminded healthcare professionals of postmarketing reports of inappropriate use of Bicillin C-R to treat patients infected with syphilis. Bicillin L-A is the only currently approved penicillin G benzathine product indicated for the treatment of syphilis and Bicillin C-R should not be administered in place of Bicillin L-A. Administration of Bicillin C-R instead of Bicillin L-A in the treatment of syphilis may result in inadequate treatment.

In addition, a BLACK BOX WARNING has been added to the prescribing information of both products to emphasize that these products should only be administered by deep intramuscular injection. They are not intended for intravenous administration and inadvertent intravenous administration of penicillin G benzathine has been associated with cardiorespiratory arrest and death. *November 2004*

Depo-Provera (medroxyprogesterone acetate injectable suspension)

FDA and Pfizer notified healthcare professionals of the addition of a BOXED WARNING along with revisions to the WARNINGS, INDICATIONS AND USAGE, PRECAUTIONS and POSTMARKETING EXPERIENCE sections of the prescribing information to include information on the loss of significant bone mineral density. Depo-Provera Contraceptive Injection is indicated only for the prevention of pregnancy in women of child-bearing potential. Bone loss is greater with increasing duration of use and may not be completely reversible. Depo-Provera Contraceptive should be used as a long-term birth control method (eg, longer than 2 years) only if other birth control methods are inadequate. *November 2004*

Mifeprex (mifepristone)

Danco Laboratories and FDA notified healthcare professionals of revisions to the BOXED WARNING and WARNINGS sections, the MEDICATION GUIDE and PATIENT AGREEMENT of the Prescribing Information to describe serious and sometimes fatal infections and bleeding that may occur following the use of Mifeprex. *November 2004*

Humira (adalimumab)

FDA and Abbott Pharmaceuticals notified healthcare professionals of revisions to the WARNINGS section of the prescribing information, indicated for the treatment of rheumatoid arthritis. These warnings include serious infections with the combined use of Humira (adalimumab) and anakinra, hypersensitivity reactions, including anaphylaxis, and hematologic events, including pancytopenia and aplastic anemia. *November 2004*

Actra-Rx and Yilishen dietary supplements

The FDA warned consumers not to purchase or to consume Actra-Rx or Yilishen, two products promoted and offered for sale on Web sites as "dietary supplements" for treating erectile dysfunction and enhancing sexual performance for men. FDA testing of Actra-Rx found that the product contained undeclared prescription-strength sildenafil. An interaction between sildenafil and certain prescription drugs containing nitrates (such as nitroglycerin) or nitrates found in illicit substances (such as amyl nitrate) may cause a significant lowering of blood pressure to an unsafe level. Consumers who have taken Actra-Rx or Yilishen should stop taking it and consult with their health care providers regarding erectile dysfunction treatment. *November 02 2004*

Reminyl (galantamine hydrobromide)

FDA, Janssen Pharmaceutica Products, and Johnson & Johnson Pharmaceutical Research & Development notified healthcare professionals of reports of medication errors involving confusion between Reminyl, a drug approved for the treatment of mild to moderate dementia of the Alzheimer's type, and Amaryl (glimepiride), a product of Aventis Pharmaceuticals, indicated for the treatment of non-insulin dependent (Type 2) diabetes mellitus. These reports include instances in which Reminyl was prescribed but Amaryl was incorrectly dispensed and administered instead, leading to various adverse events including severe hypoglycemia and one death. *October 2004*

Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications

The Food and Drug Administration issued a Public Health Advisory, asking manufacturers of all antidepressant drugs to revise the labeling for their products to include a boxed warning and expanded warning statements that alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents, and additional information about the results of pediatric studies. FDA also informed these manufacturers that it has determined that a Patient Medication Guide (MedGuide), which will be

Continued on page 5

A Fatal Drug Interaction

Case Report:

Contributed By: S. Eliza Halcomb MD, Lewis Nelson MD. New York City Poison Control Center.

A 54-year-old man was brought into the emergency department complaining of crushing substernal chest pain after using cocaine earlier that morning. The pain was of sudden onset, lasting for three hours, aggravated by exertion and relieved by rest. He also complained of nausea and vomiting as well as recent three pillow orthopnea and paroxysmal nocturnal dyspnea. His past medical history was significant for hypertension. He denied taking any medications and had no known drug allergies. His social history was remarkable for a 30-pack year smoking habit and frequent cocaine use.

On examination, he was alert and oriented sitting up in bed. His blood pressure was 145/95 mmHg, heart rate was 115/min, breathing at 20/min and he was afebrile with a temperature of 96.8°F. His cardiovascular exam was notable for tachycardia and jugular venous distension. His lungs were clear to auscultation bilaterally, with no notable wheezes or crackles. His abdominal and neurologic exams were normal.

What are the initial steps to take in the care of this patient?

The symptoms described by this patient are concerning for an acute coronary syndrome such as unstable angina or myocardial infarction. The initial management, particularly in this patient experiencing subjective breathing difficulties, should include assurance of adequate gas exchange (airway and breathing) as well as circulation.

These issues each need to be addressed to minimize damage to ischemic cardiac muscle. The initial interventions in this case included placing the patient on oxygen, placing an intravenous catheter and placing the patient on a monitor. He then had an ECG done and labs sent.

What are the pharmacologic agents used to treat acute coronary syndromes?

All patients presenting with chest pain believed to be of cardiac origin should receive an aspirin and nitroglycerin, unless contraindicated. Aspirin has anti-platelet effects that prevent clot formation and nitroglycerin has vasodilatory effects that help increase blood flow to potentially ischemic myocardium. In addition, intravenous morphine alleviates pain, which reduces the patient's sympathetic tone and decreases the adverse hemodynamic effects of pain and dyspnea. Although improving blood flow to the heart is paramount, a critical additional intervention includes reducing the oxygen requirement of the heart. Beta-adrenergic antagonists alleviate the patient's tachycardia by preventing the binding of endogenous catecholamines on the cardiac ß-1 adrenergic receptors. Blockade of these receptors has both negative ionotropic and chronotropic effects leading to reduction of cardiac work and oxygen consumption as well as a reduction in the mean arterial blood pressure. Note that because there are ß-2 receptors on the skeletal muscle vasculature, the use of non-selective ß-adrenergic antagonists does not typically result in a precipitous fall in mean arterial blood pressure. That is, since stimulation at these receptors produces vasorelaxation, mild peripheral vasoconstriction may occur through their antagonism.

Are there any concerns about using the traditional pharmacologic agents in this setting?

This patient had used cocaine on the day of presentation. Cocaine is a centrally acting sympathomimetic agent. Its mechanism of action is to prevent the reuptake of norepinephrine and other biogenic amines at nerve endings, which, among other things, increases the outflow of activity via the peripheral sympathetic nerves. Alpha-adrenergic receptor stimulation is prominent from the peripherally-released norepinephrine in patients with high sympathetic tone, resulting in vasoconstriction and hypertension.

Given its central nervous system site of action, the most effective way to treat the clinical manifestations of cocaine is with sedation, typically with benzodiazepines. By decreasing central nervous system activity, there is a concomitant reduction in peripheral sympathetic outflow. If this does not produce sufficient hemodynamic control, vasodilators such as nitroprusside, or preferentially phentolamine, an α-adrenergic antagonists, may be useful.

There are major concerns about using ß-adrenergic antagonists to reduce the heart rate or blood pressure

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A Fatal Drug Interaction

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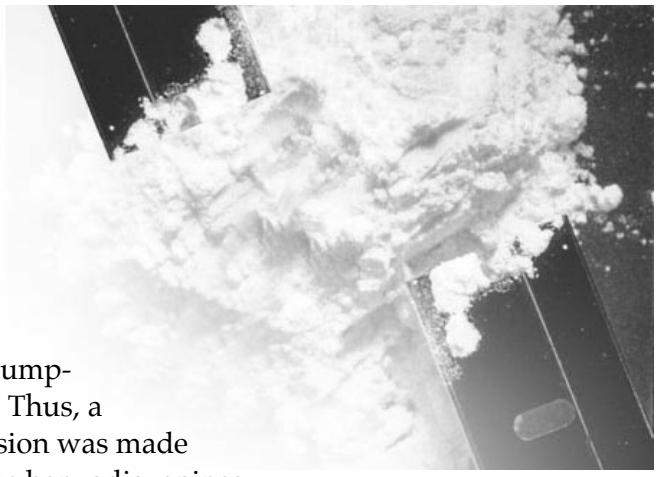
in patients with cocaine-related ischemia. Since cocaine causes α-mediated vasoconstriction, ß-adrenergic antagonism may block ß-2 mediated vasodilation. Thus, the concomitant use of ß-adrenergic antagonists may result in life-threatening hypertension and associated complications as a result of "unopposed alpha" vasoconstriction. That is, since cocaine causes its peripheral hemodynamic effects through the release of norepinephrine from the sympathetic nervous system, and since norepinephrine has a potent α-adrenergic agonist effect, the use of non-selective (and probably all) ß-adrenergic antagonists eliminate the small amount of ß-2 mediated vasodilatation. Thus, the α-adrenergic effects remain and produce unopposed vasoconstriction. A 1990 study by Lange et al. found that administration of propranolol in the setting of low dose cocaine use resulted in increased coronary vascular resistance and a reduction in the diameter of the coronary artery. A 1993 study by Boehrer et al showed that labetolol administration in the setting of low dose cocaine use caused an increase in mean arterial blood pressure, no change in heart rate and a decrease in coronary artery area, and clearly demonstrated coronary artery vasoconstriction angiographically. That is, labetolol, despite is α-adrenergic antagonistic effects, is no better than propranolol.

Case Continuation

This patient's pain was completely relieved with the administration of aspirin, however he remained tachycardic and hypertensive, which concerned the clinician due to the aforementioned increase in oxygen



consumption. Thus, a decision was made to use benzodiazepines to treat his heart rate and blood pressure. However, this patient's heart rate and blood pressure remained slightly elevated one hour after his arrival to the emergency department (about 6 hours after his cocaine use). A decision was made to administer intravenously a low dose (2.5 mg) of metoprolol. This lowered the systolic blood pressure to 125 mmHg and his heart rate dropped from 115 to 105. Another 2.5 mg metoprolol was administered minutes later, after which the patient immediately complained of severe chest pain, vomited and collapsed. CPR was commenced with no return of spontaneous circulation.

This was an unfortunate case in that the physician felt that since the patient had used cocaine 6 hours prior to arrival, it was probably safe to treat with a ß-adrenergic antagonist. However, it must be noted that although cocaine is rapidly eliminated from the body through metabolism, it has several vasoactive metabolites that may be active for at least a day postexposure. Therefore, the use of ß-adrenergic antagonists cannot be recommended in patients with symptoms and signs of coronary ischemia in the setting of recent cocaine use. When it is safe to use ß-adrenergic antagonists remains a matter of debate. However, give the limited data that early ß-blockade is better than subsequent administration it seems prudent to avoid their use in the first 24 hours post-cocaine use.

Select References.

Boehrer J. et al. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. Am J Med 1993;94:608-610.

Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. J Pharmacol Exp Ther 1981;217:350-356.

Lange RA et al. Potentiation of cocaine-induced coronary vasoconstriction br beta-adrenergic blockade. Ann Intern Med 1990:112:897-903

Tox Trivia Answers

1. chloroform
2. Third
3. gas chromatography / mass spectrometry

NYPC Tidbits Answers

1. dextromethorphan
2. methanol
3. cherry red skin

Crossword Answers

Across: 1. Sodiumchloride 4. Elementalmercury 7. Tetrahydrolazine 9. Erythromycin 10. Methanol; *Down:* 2. Diphenhydramine 3. Dextromethorphan 5. Carbonmonoxide 6. Ethyleneglycol 8. Camphor

SPI CORNER TOPIC:
TOXIC MOLD

Contributed by: Margo M. Spain RN, CSPI, Mary Halsey-Claps RN, CSPI, Central New York Poison Center, Syracuse, NY

Summer is over, windows are closed, the poison centers call volume regarding toxic molds is increasing. After sifting through the volumes of information referring to molds, we felt some information needed clarification.

What is mold?

Mold is everywhere. It has characteristics of plants and animals. Mold is a visible colony of fungi. Most fungi are saprophytes which breakdown decaying materials then absorb the decayed material as nutrition. They serve a critical role in the ecology of decaying materials. Molds grow anywhere there is sufficient moisture and nutrient source indoor or outdoor environments over a broad spectrum of temperatures. Dirt, dust, wood, paper, paint, and insulation are common materials of nutrition combined with moisture. Mold in itself is not a problem when the source is in the normal interchange of outside and indoor air. When the balance is off and increased moisture rises to an ideal environment for amplification of mold growth which promote as a byproduct mycotoxins or bacterial volatile organic compounds.

Three common types of molds are zygomycetes, ascomycetes and basidiomycetes that contaminate buildings. The most common indoor molds are Cladosporium, Penicillium, Aspergillus, Stachybotrys chartarum, and Alternaria. The Stachybotrys atra and the Aspergillus versicolor are known to produce potent toxins under certain circumstances. Stacybotrys chartarum and Aspergillus prefer cellulose on wall board.

Health Effects

Mold exposure does not always present a health problem , however some people are sensitive and exposure can result in infections, hypersensitivity, irritant or toxic reactions. Hypersensitive reactions can go on to cause allergic rhinitis, asthma or hypersensitivity pneumonitis. Although certain mycotoxins are known to be responsible for health effects, little information is available on others.

Two conditions involve a more intense immunologic response to fungi: allergic bronchopulmonary aspergillus (ABPA) and allergic fungus sinusitis (AFS). ABPA occurs in patients with underlying asthma and cystic fibrosis who develop Aspergillus colonization of the airway.

In December 1994 and January 1997, a cluster of 10* infants from Cleveland, Ohio, with Acute Idiopathic Pulmonary Hemorrhage (AIPH) also referred to as Pulmonary Hemosiderosis were found to reside in the same postal tracts and had one or more hemorrhagic episodes, resulting in one death . Preliminary results of a CDC case-control study indicated that hemorrhage was associated with 1) major household water damage during the 6 months before illness and 2) increased levels of measurable household fungi, including the toxin- producing mold Stachybotrys chararum.

To date, a possible association between Acute Idiopathic Pulmonary Hemorrhage (AIPH) among infants and the stachybotrys chartarum has not been established. The CDC will continue to investigate and consider possible associations between AIPH and mycotoxin exposure.

Testing

Generally, it is not necessary to identify the species of mold growing in a residence.

The CDC does not recommend routine sampling for molds. Reliable sampling for mold can be expensive and standards for judging what is and what is not an acceptable or tolerable quantity of mold has not been established. In certain instances, such as cases where health concerns are an issue, litigation is involved, or the source(s) of the contamination is unclear, sampling may be considered as part of a building evaluation.

The Health Department, although it will not do testing, will send in a county sanitation representative to observe the mold and give recommendations. They will follow up with the landlord and perform a home inspection to ensure that the mold situation has been corrected.

Remediation of Molds

If mold is visible, then it should be remediated, regardless of what species is present. If the building smells moldy, but you cannot see the source you should suspect a hidden mold problem. Moisture control is the key to mold control. Mold will often grow in damp or wet areas indoors. Common sites include bathroom tiles, under water damaged floors and carpeting, behind wallpaper and paneling and

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FDA Safety Summaries

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given to patients receiving the drugs to advise them of the risk and precautions that can be taken, is appropriate for these drug products. October 2004

Remicade (infliximab)

FDA and Centocor notified healthcare professionals of revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information for Remicade, indicated for the treatment of rheumatoid arthritis and Crohn's disease. In controlled studies of all TNF-blocking agents, including Remicade, more cases of lymphoma have been observed among patients receiving the agents than among control group patients. Malignancies have also been observed in open-label, uncontrolled clinical studies at a rate several-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma. FDA has recommended a warning concerning malignancy be added to the labeling for all therapeutic agents that block TNF. *October 2004*

Levoxyl (levothyroxine sodium)

FDA and King Pharmaceuticals notified healthcare professionals of revisions to the PRECAUTIONS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections of labeling, describing reports of choking, gagging, tablets stuck in throat and dysphagia while taking Levoxyl. These reports have predominately occurred when Levoxyl tablets were not taken with water. It is recommended that Levoxyl tablets be taken with a full glass of water. *September 1,7 2004*

Zometa (zoledronic acid) Injection

FDA and Novartis notified healthcare professionals of revisions the PRECAUTIONS and ADVERSE REACTIONS sections of labeling, describing spontaneous reports of osteonecrosis of the jaw mainly in cancer patients, who have received bisphosphonates as a component of their therapy. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). *September 24, 2004*

Vioxx (rofecoxib)

Merck & Co., Inc. announced a voluntary withdrawal of Vioxx (rofecoxib) from the U.S. and worldwide market due to safety concerns of an increased risk of cardiovascular events (including heart attack and stroke) in patients on Vioxx. Vioxx is a prescription COX-2 selective, non-steroidal anti-inflammatory drug (NSAID) that was approved by FDA in May 1999 for the relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms, and was later approved for the relief of the signs and symptoms of rheumatoid arthritis in adults and children. *September 30, 2004*

SPI CORNER TOPIC: TOXIC MOLD

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basement walls.

The Health Department and the CDC recommend that in most cases mold can be removed by a thorough cleaning with a detergent, bleach and water solution. If there is an extensive amount of mold, professional remediation may be required. Persons cleaning mold should wear protective clothing, rubber gloves, eye protection, and a N95 dust mask or respirator. The area should be well ventilated.

Public awareness has increased regarding toxic molds. Litigation and proposed legislation have been put forth in an attempt to bring increased action to remedy the health risk and property damage caused by this national problem.

References:

March 10, 2000: MMWR Update: Pulmonary Hemorrhage/Hemosiderosis Among infants Cleveland, Ohio, 1993-1996

Guidance for Clinicians on the recognition and management of health effects Related to Mold Exposure and Moisture Indoors - September 30, 2004

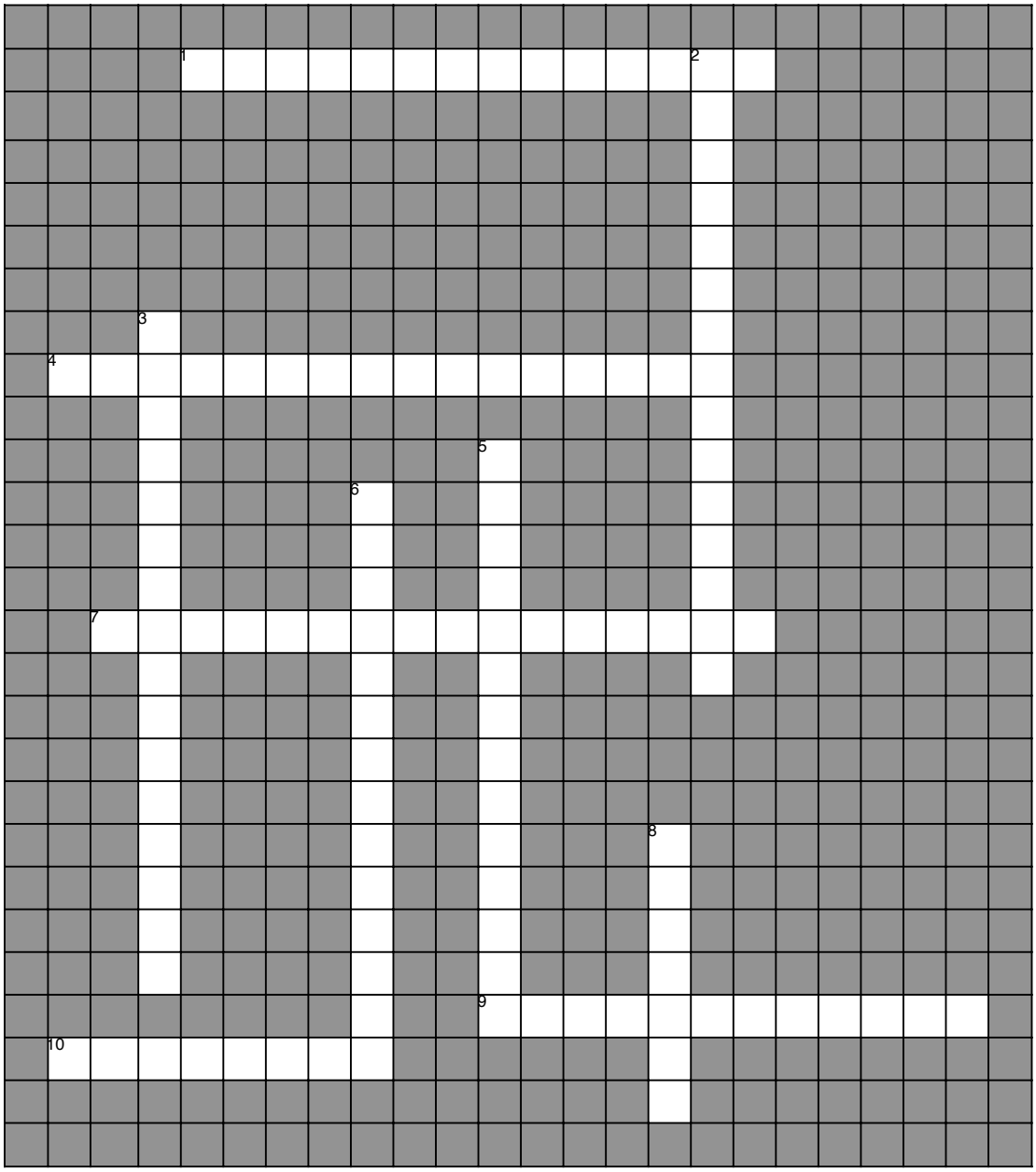
Report to the CDC Working Group on Pulmonary hemorrhage/Hemosiderosis- June 17, 1999

CDC/NCID Division of Bacterial and Mycotoxic Diseases: Fungal Diseases

TOXICOLOGY CROSSWORD

WINTER TOXINS

Contributed by: Laurie Piwinski, RN, CSPI Central New York Poison Control Center, Syracuse, NY



Across

1. Ingredient in ice-melting crystals that may cause initial vomiting when ingested
4. Substance that is non toxic when swallowed if a thermometer breaks in the mouth
7. Ingredient in ophthalmic and nasal preparations that has a clonidine-like effect after ingestion
9. Antibiotic with many drug interactions due to it's ability to inhibit CYP 3A4
10. Deadly toxin in windshield washer fluid

Down

2. Over the counter allergy medication that may cause lilliputian hallucinations in overdose
3. Common over the counter medication abused by teens
5. Odorless, tasteless gas; #1 poisoning killer
6. Ingredient in radiator antifreeze responsible for metabolic acidosis, renal failure and death in poisonings
8. Toxin in liniments and vaporizer additives that can cause seizures after ingestion

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