



January 2005

The NY State Poison Centers

TOXICOLOGY

A Quarterly Publication • Vol. IX No. 5

LETTER

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 • <http://wnypoison.org>

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: 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 Ninth 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

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 health-care 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 health-care 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, intra-

venous 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 β -1 adrenergic receptors. Blockade of these receptors has both negative inotropic 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 β -2 receptors on the skeletal muscle vasculature, the use of non-selective β -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 β -adrenergic antagonists to reduce the heart rate or blood pressure

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in patients with cocaine-related ischemia. Since cocaine causes α -mediated vasoconstriction, β -adrenergic antagonism may block β -2 mediated vasodilation. Thus, the concomitant use of β -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) β -adrenergic antagonists eliminate the small amount of β -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 labetalol 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, labetalol, despite its 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

Tox Trivia Answers • •

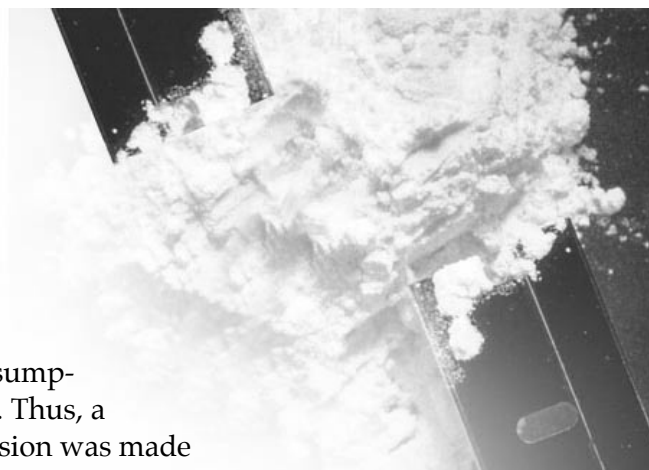
1. chloroform
2. Third
3. gas chromatography / mass spectrometry

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. Carbon-monoxide 6. Ethyleneglycol 8. Camphor



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 β -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 β -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 β -adrenergic antagonists remains a matter of debate. However, give the limited data that early β -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 by beta-adrenergic blockade. *Ann Intern Med* 1990;112:897-903

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. Stachybotrys 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 Idio-

pathic 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 chartarum.

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

Continued from page 2

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

Levoxyll (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 Levoxyll. These reports have

predominately occurred when Levoxyll tablets were not taken with water. It is recommended that Levoxyll 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

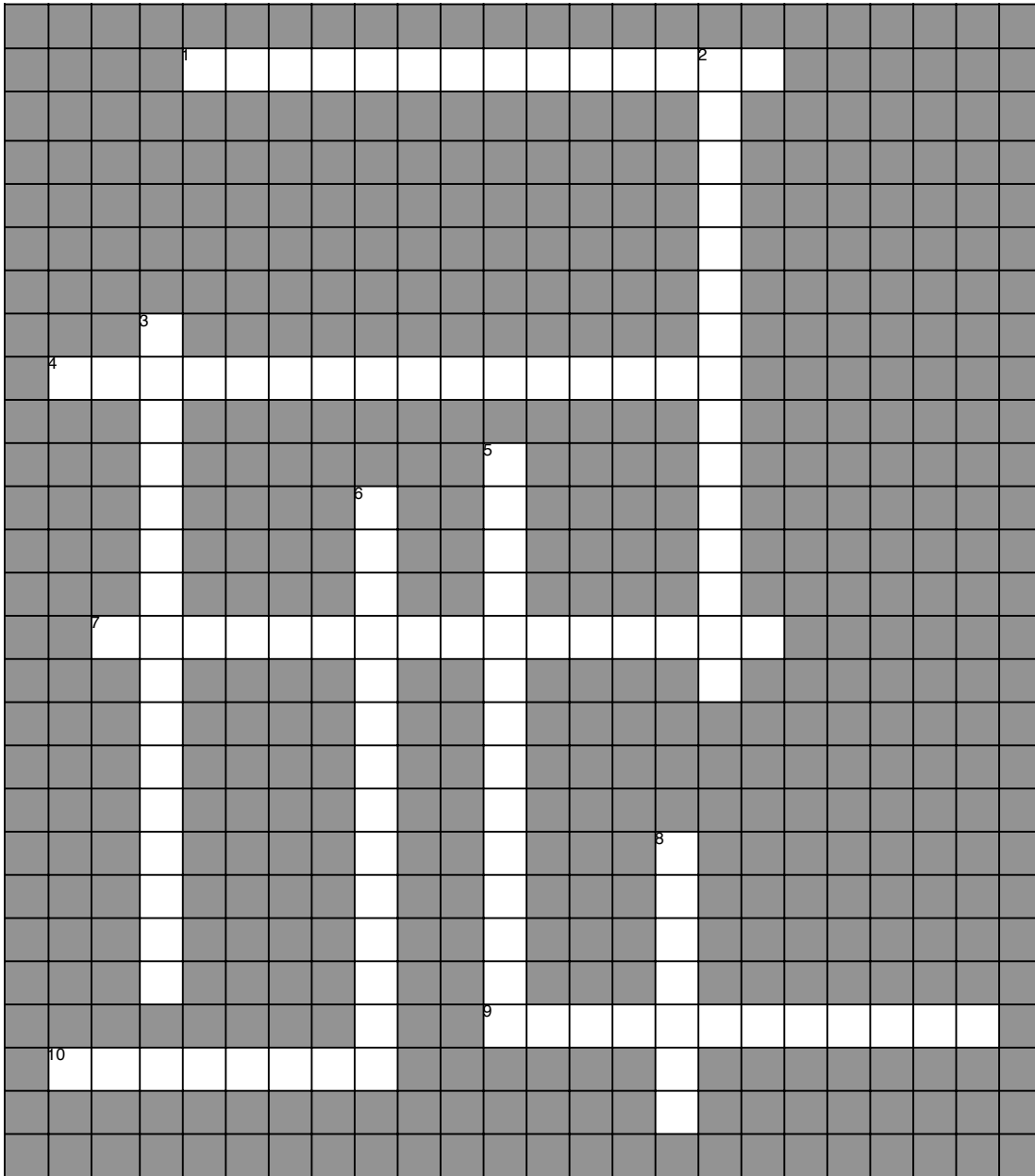
Report to the CDC Working Group on Pulmonary hemorrhage/Hemosiderosis- June 17, 1999

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



UPSTATE MEDICAL CENTER
750 East Adams Street
Syracuse, NY
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NYC: Consultants Case Conference • The first Thursday of the Month from 2-4pm

LI: March 30, 2005: Sports Toxicology
David Lee, M.D., ABEM, ABMT

April 27, 2005: Weapons Of Mass Destruction
Robin McFee, D.O., MPH

May 23, 2005: Dangers of Drug Interactions And Adverse Drug Reactions In Geriatric Patients
Irving Gomolin, M.D.

June 29, 2005: Recognition and Management of the Most Deadly Poisons Around
Heather Long, M.D., ABEM

Times: 12:15 PM-1:45 PM

Location: New Life Conference Rooms B&C, Winthrop-University Hospital, 259 First Street, Mineola, Long Island, New York 11501. Pre-Registration is required. Please contact *Denis Jao* at 516-663-2650 if interested in attending. Both Telephone and Televideo broadcasts will be available.

Please call administrative telephone numbers for more information.

Tox Trivia • •

1. What phenomenon is characteristic of ciguatera?
2. What vitamin is in roseheads?
3. What is the toxin in amanita pantheria?

NYPC Tidbits • •

1. What Shakespearean character dies from a snakebite?
2. What state introduced the lethal injection as a form of execution in 1982?
3. What car manufacturer produced a car known as the Stingray?

Answers on page 6

Paxil CR (paroxetine hydrochloride)

Avandamet (rosiglitazone maleate + metformin hydrochloride)

FDA and the Department of Justice have seized the remaining stocks of Paxil CR and Avandamet tablets manufactured by GlaxoSmithKline, Inc. Manufacturing practices for the two drugs, approved to treat depression and panic disorder (Paxil CR) and Type II Diabetes (Avandamet), failed to meet the standards laid out by FDA that ensure product safety, strength, quality and purity. *March 4, 2004*

Crestor (rosuvastatin calcium)

FDA issued a public health advisory describing revisions to the WARNINGS, DOSAGE AND ADMINISTRATION, CLINICAL PHARMACOLOGY, and PRECAUTIONS sections of the labeling. The revisions include results from a Phase 4 pharmacokinetic study in Asian-Americans and highlight important information on the safe use of Crestor to reduce the risk for serious muscle toxicity (myopathy / rhabdomyolysis), especially at the highest approved dose of 40 mg. *March 2, 2005*

Tysabri (natalizumab)

FDA issued a public health advisory to inform patients and health care providers about the suspended marketing of Tysabri (natalizumab) due to two serious adverse events reported with its use. FDA received reports of one confirmed, fatal case and one possible case of progressive multifocal leukoencephalopathy (PML) in patients receiving Tysabri for multiple sclerosis. *February 28, 2005*

Gabitril (tiagabine)

FDA and Cephalon, Inc. notified healthcare professionals and the public that a Bolded Warning has been added to the labeling for Gabitril (tiagabine) to warn prescribers of the risk of seizures in patients without epilepsy being treated with Gabitril. *February 14, 2005*

Phenergan (promethazine hydrochloride)

FDA and Wyeth notified healthcare professionals of revisions to the CONTRAINDICATIONS, WARNINGS/Use in Pediatric Patients, and DOSAGE AND ADMINISTRATION sections of the prescribing information for Phenergan. Phenergan is contraindicated for use in pediatric patients less than two years of age because of the potential for fatal respiratory depression. *January 21, 2005*

Adderall XR (amphetamine)

FDA issued a Public Health Advisory to notify healthcare professionals that Health Canada, the

Canadian drug regulatory agency, has suspended the sale of Adderall XR in the Canadian market. Adderall XR is a controlled release amphetamine used to treat patients with Attention Deficit Hyperactivity Disorder (ADHD). The Canadian action was based on U.S. post-marketing reports of sudden deaths in pediatric patients. *February 10, 2005*

Agrylin (anagrelide hydrochloride)

Shire and FDA notified healthcare professionals about changes to the CONTRAINDICATIONS and WARNINGS sections of the prescribing information for Agrylin (anagrelide hydrochloride), a medication approved for the treatment of thrombocytopenia secondary to myeloproliferative disorders to reduce platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events. Pharmacokinetic studies have revealed an 8-fold increase in total exposure (AUC) to anagrelide hydrochloride in patients with moderate hepatic impairment. *January 2005*

Invirase (saquinavir mesylate capsules and tablets)

Fortovase (saquinavir soft gelatin capsules)

Roche and FDA notified healthcare professionals about an Important drug interaction warning. Drug-induced hepatitis with marked transaminase elevations has been observed in healthy volunteers receiving rifampin 600 mg once daily in combination with ritonavir 100 mg/saquinavir 1000 mg twice daily (ritonavir boosted saquinavir). *February 2005*

ZyPREXA (olanzapine)

Eli Lilly and FDA notified healthcare professionals reports of medication dispensing or prescribing errors between the atypical antipsychotic ZyPREXA (olanzapine), indicated for the short-term and maintenance treatment of schizophrenia and for the short-term treatment of acute mixed or manic episodes associated with Bipolar I Disorder, and the antihistamine ZYRTEC (cetirizine HCl) marketed by Pfizer, indicated for the treatment of allergic rhinitis or chronic urticaria. *January 26, 2005*

IV Flush Brand of Preloaded Syringes Containing Heparin or Sodium Chloride

FDA is issuing a nationwide alert against the use of all lots of preloaded syringes containing either heparin or sodium chloride intravenous catheter flushes manufactured by the IV Flush, LLC and distributed by Pinnacle Medical Supply, of Rowlett, Texas, because they lacked proper FDA clearance for

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Poisonous Plants in New York State

Case Report:

Contributed By: Ruth A. Lawrence, MD, Medical Director – Finger Lakes Poison Center

Are There Any Poisonous Plants In The State Of New York?

The toxicology literature has been filled with reports of plant exposures that have appeared in the data collected by the American Association of Poison Centers. Many of these articles have indicated that since many of these reported exposures did not appear to result in any symptoms or morbidity that these plants are not toxic. Unless the plant is carefully identified and a close assessment of actual exposure, i.e. a real ingestion is confirmed, interpreting the outcome is fallacious. There are toxic plants in this state of New York and they are readily available in cultivated yards as well as meadows, fields and woods.

Plants from the standpoint of toxicity can be classified in three categories. The first is edible; the second is non-toxic but inedible and thirdly toxic. Many plants including the common tomato and potato, which are in the solanine family, have both edible and poisonous parts. This is also true of rhubarb where the stalks are edible and the leaves are highly toxic due to the high concentration of oxalate. It is appropriate to be familiar with the most toxic plants in one's immediate geographic area. While it may not always be possible to identify definitively a plant by telephone with the description from a frantic mother, it should be possible to rule out toxic plants with similar descriptions.

Exposures

Plant exposures and potential toxicity can occur from contact, ingestion and by inhalation. The most common contact dermatitis from plants is Poison Ivy and this plant is usually well recognized with its triple leaf formation, its vine like characteristics and its oily substance, which causes a severe blistering rash. Poison Sumac and Poison Oak cause similar rashes and are usually found in the woods and should be recognizable. Poison Oaks are in the species of *Toxicodendron diversilobum*. Poison Ivy is *Rhus radicans*. In the same group of allergic contact dermatitis is the cashew, the mango tree and the smoke tree.

A newer plant in this group of allergic dermatitis is a plant that causes photo dermatitis and was indeed imported from Russia years ago as a good hedging plant for fields. It is commonly known as Russian hogweed or giant hogweed (*Helleborus mantegazzianum* Sommier). Giant hogweed looks like giant Queen Anne's

Lace standing sometimes ten feet tall. The flowers are as big as dinner plates and it is a very enticing intriguing plant for children who often like to play in and around it or cut its stalks to make blow guns. It is in the same family as Queen Anne's Lace, cow parsnip, fig and lime. The rash that is caused by contact with hogweed however is very photosensitive and reappears every time the skin is exposed to sunlight even as long as a year later. The rash is not unlike that of poison ivy except that it is both painful and itchy and has often has a hemorrhagic base. Its constant recurrence is especially irritating. Victims must avoid skin exposure to sunlight.

Toxicity by inhalation is a large family of plants with pollen, seeds and other particles in the air that cause allergic reactions in some individuals.

To help the poison center determine the potential hazard in the ingestion of a berry, it is helpful to have an indication that the berry was in the mouth, was chewed, and appears on the teeth and other traces as well. General estimation of the hazard of a given exposure is that six or more berries have the potential of being serious. Furthermore the amount of leaf ingested would have to exceed a half-dollar in size to present a risk of significant toxicity.

Nightshade

Nightshade is a member of the solanum species. The family is Solanaceae. There are a number of plants in this family, most of which are poisonous and many which are available in our region and sometimes in our homes. The most notorious is deadly nightshade or black nightshade (*S. americanum* or *S. nigrum*). Deadly nightshade is very toxic. It is different from ordinary common nightshade with the following characteristics: the plant is less aggressive, is less likely to have long vines and wrap itself around bushes and trees but the leaf shapes are similar. The important differential is that the flowers are white and the pistil is yellow. They are the same 3-5mm size and bloom at the same time as berries are ripening. The berries are black when ripe and contain considerably more of the toxic principle, solanine glycoalkaloids.

Black nightshade is a native to Europe but has been found in the United States and has been found in New York State especially upstate New York. Common nightshade is one that plagues most of New York

Continued on page 4

States gardens and yards is an aggressive vine that winds itself around other plants, bushes and trees, has heart shaped and tri-shaped leaves and a characteristic tiny purple flower with a yellow stamen. It too has flowers while berries are ripening; the berries are bright red and hang in a droop. Two to three of these berries may cause mouth irritation but probably little in the way of systemic symptoms. Two to three black nightshade berries could have serious morbidity. Symptoms are gastric irritation, general GI tract irritation with vomiting and diarrhea and may even be confused with gastroenteritis. However, the most disturbing symptoms are those of behavior changes and anticholinergic symptoms of increased temperature, flushed face, dilated pupils and irrational behavior. Other members of this plant family are the tomato and the potato. Sprouts from a potato are toxic and during the potato famine of Ireland caused many deaths. The indoor plant, the Jerusalem Cherry, is in the same family and causes similar symptoms. It is easier to diagnose because it is a houseplant and usually there are only one or two fruit on the plant, which are easily counted. One "cherry" could cause symptoms in a young child.

Nightshade is a simple telephone diagnosis by the shape of the leaves, the droop of berries and the classic tiny flower with the yellow stamen. The public often describes it as a vine, a bush or a tree depending on what it has chosen to wrap itself around.

Polkweed

Polkweed is *Phytolacca americana* and is a member of the family of *phytolaccaceae*. It goes by other names such as inkberry, Indian polk, red weed. Polkweed is a confusing plant because early in the spring it's young sprouts and stems are boiled and safely eaten after cooking in several waters. The very mature black inky berries are also relatively non-toxic. In between those times however, there is significant toxicity due to *phytolaccatoxin* and related triterpenes. A common error even among knowledgeable gardeners is mistaking a polk root for parsnip or horseradish, both of which are edible, while the polk root is extremely toxic. The classic recognizable characteristics of this plant, which grows from Maine to Minnesota and throughout New York State is the large perennial rootstock from which stout purplish branching leaf stalks emerge. It can grow up to twelve feet in height. The stems, while green initially turn red as the toxin increases in concentration. The single leaves are four to twelve inches long; the flowers are greenish white to purplish, small and appear on a short stalk. The dark berries are purplish to black and are attached to

the stalk by a very short stem. The berries before they become fully ripe look like miniature green pumpkins and are toxic.

The symptoms from consuming any toxic part of the polk weed are usually delayed for two hours or so and begin with nausea and severe gastroenteric cramps, profuse sweating, persistent vomiting and later diarrhea. The symptoms may continue for forty-eight hours. Management involves symptomatic treatment for pain and the replacement of fluids. Children usually require hospitalization. Many adults have been hospitalized for consuming the root or eating the leaves when they are mature and toxic.

The Castor Bean Plant

Another toxic ornamental plant that has reappeared in the state of New York is the Castor Bean plant, which is *Ricinus communis*. Family *euphorbiaceae*. Other popular names are the wonder tree or the ricin. This majestic plant grows over fifteen feet high has large lobed leaves sometimes three feet across. Its spiny seedpods form clusters along spikes. The pods contain plump seeds with unusually beautiful mottled brown on white coloring. The seed has a very pleasant taste but contains the toxin ricin, plant toxin, lacticin (toxalbumin), which inhibits protein synthesis in the intestinal wall. The oil when extracted from this plant is the castor oil, which is a powerful but non-toxic cathartic. When the seeds are eaten or large amounts of the rest of the plant, symptoms occur after a latent period of a several hours. There is nausea, vomiting and diarrhea with massive fluid and electrolyte loss and intestinal dysfunction. The ingestion can be fatal because of hypovolemia and electrolyte abnormalities. It has been estimated that the ingestion of as few as two of these seeds can be fatal. Ricin of course has been identified as one of the most toxic poisons in every day terrorism.

Angel Trumpet

Angel Trumpet (*brugmansia suaveolens*) is a beautiful majestic shrub that has become very popular in New York State gardens. It is a small bush with classic trumpet shaped flowers. It is also known as Jimson weed, Mad Apple and Thorn Apple. It causes Belladonna syndrome. The white flowers are funnel shaped, large and showy and point upward. The prickly fruits are capsules about two inches long which split open when mature and dry along four seams to expose the numerous kidney shaped brownish black seeds. There are other varieties, which have lavender or red flowers, which often appear as a vine on telephone poles.

The whole plant is toxic including the nectar but the seeds are most commonly ingested in unintentional poisonings. The dried leaves have been used by individuals seeking a delirious reaction. The toxin is Belladonna alkaloids. The symptoms are the classic Belladonna dry mouth, mydriasis, dry warm skin, red face, tachycardia and delirium with hallucinations. Children are most severely affected, sometimes so severely as to require anticholinergic physostigmine.

BERRIES

Toxic	Non-toxic/inedible
Nightshade (especially black)	Honeysuckle
Yew (Taxus)	Fully ripe poke berry
Lily of the Valley	
Evergreen bittersweet (euonymus)	
Holly Berries	
Mistletoe	

PLANTS THAT CAUSE SKIN IRRITATION

Plants that cause contact dermatitis
Hydrangea
Hyacinth
Tulip
Plants that contain Raphides
Dumbcane
Pothos
Boston Ivy
Plants that produce phytophotodermatitis
Queen Ann's Lace
Giant Hogweed
Lime
Plants that have stinging hairs or detachable needles
Stinging Nettle
Stinging Lupine
Plants that contain irritant sap or latex
Snow on the mountain
Crown of thorns
Plants causing allergic contact dermatitis
Poison Ivy
Poison Oak
Cashew

Note: These are examples and not exclusive lists.

The duration of action of Belladonna alkaloids is longer than that of the physostigmine so repeated administration has been required.

This is only a brief review of some of the more attractive, toxic and common plant exposures in the State of New York. Absence from this list does not imply that the plant is non-toxic. Poison centers should be familiar with the local culprits and be able to rule out toxicity in the event of a plant exposure.

References:

Lampe K, McCann MA, AMA Handbook of Poisonous and Injurious Plants, Chicago Review Press 1985

Gridley Peterson M, How to Know Wild Fruits, Dover Publications, 1973

Kinghorn A, Toxic Plants, Columbia University Press, 1979



marketing. FDA and the company have also been informed of *Pseudomonas fluorescens* (*P. fluorescens*) infections in patients possibly caused by the heparin flushes. PDATE February 4, 2005

Viramune (nevirapine)

FDA issued a public health advisory to inform health care providers and patients about recent safety-related changes to the nevirapine (Viramune®) label and about appropriate use of HIV triple combination therapy containing nevirapine, a treatment option in the United States which is increasingly being used globally. The Indications and Usage section now recommends against starting nevirapine treatment in women with CD4 + cell counts greater than 250 cells/mm³ unless benefits clearly outweigh risks. This recommendation is based on a higher observed risk of serious liver toxicity in patients with higher CD4 cell counts prior to initiation of therapy. January 19, 2005

Methylin CT (Methylphenidate HCl Chewable Tablets)

[01/19/2005] FDA and Alliant Pharmaceuticals notified healthcare professionals and consumers of the voluntary recall of one lot of Methylphenidate HCl Chewable Tablets, 5 mg strength, indicated for Attention Deficit Hyperactivity Disorder and Narcolepsy. After testing and evaluation, Alliant found that lot number #AMT50402A [expiration date April 2006] might contain up to three times the active ingredient, and elected to recall the medication as it could pose serious health risk for some patients. UPDATE 02/10/2005

Aranesp (darbepoetin alfa)

FDA and Amgen notified healthcare professionals of revisions to the WARNINGS and PRECAUTIONS

sections of the prescribing information for Aranesp, indicated for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies. This safety information alerts physicians to the adverse effects observed with other products in this class in association with off-label dosing strategies. Two recent investigational studies with other erythropoietic products permitted or required dosing to achieve hemoglobin levels of greater than 12 grams per deciliter. An increased frequency of adverse patient outcomes, including increased mortality and thrombotic vascular events were reported in these studies. January 11, 2005

Cordarone (amiodarone HCl)

FDA and Wyeth notified pharmacists and physicians of a new Medication Guide for Cordarone (amiodarone hydrochloride tablets). The FDA regulation 21CFR 208 requires a Medication Guide to be provided with each prescription that is dispensed for products that FDA determines pose a serious and significant public health concern. December 30, 2004

Avastin (bevacizumab)

FDA and Genentech notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS, ADVERSE EVENTS, and DOSAGE AND ADMINISTRATION sections of the Avastin labeling. Avastin, used in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. Arterial thromboembolic events, including cerebral infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), and angina, occurred at a higher incidence in patients receiving Avastin in combination with chemotherapy as compared to those receiving chemotherapy alone. January 5, 2005

Tox Trivia Answers • •

1. Dry ice phenomenon
2. Vitamin C
3. Ibotenic acid and mucilol

NYPC Tidbits Answers • •

1. Cleopatra
2. Texas
3. Chevrolet

Crossword Answers • •

Across

4. inhalation
8. ethylene glycol
9. pokeweed
10. giant hogweed

Down

1. black nightshade
2. kidney
3. angel trumpet
5. calcium oxalate
6. sweet
7. fomepizole

SPI CORNER TOPIC: ETHYLENE GLYCOL TOXICITY & ASSAY

Contributed by: Sharon Ternullo, Pharm. D., CSPI, Drug Information Coordinator, Finger Lakes Regional Poison and Drug Information Center

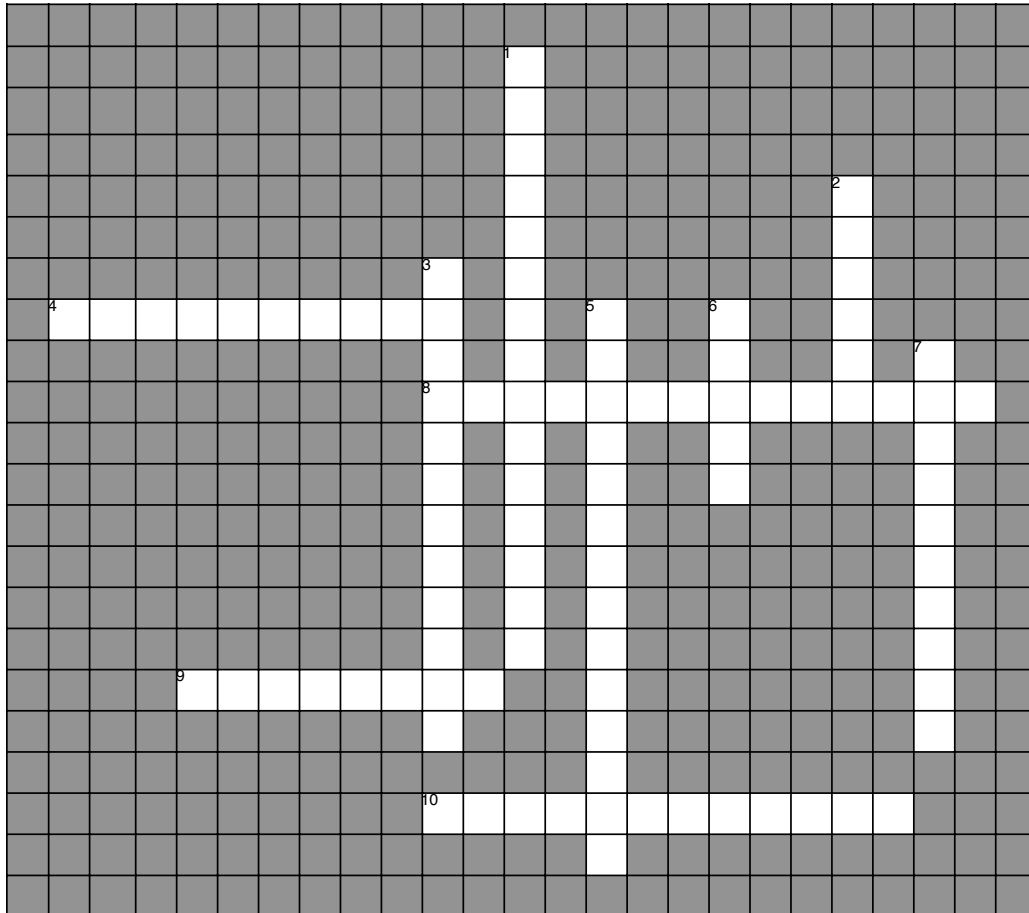
Ethylene glycol is a sweet, colorless, odorless liquid that is very palatable to animals and children. As little as 2 tablespoons of ethylene glycol can be fatal in adults and one fourth of that in children. The primary source of ethylene glycol is antifreeze, which contains between 95% and 98% ethylene glycol. Ethylene glycol is rapidly absorbed from the gastrointestinal tract and widely distributed to all tissues. Metabolism is primarily in the liver, and to a lesser degree in the kidneys. The limiting step in metabolism is the conversion of ethylene glycol to glycoaldehyde by alcohol dehydrogenase. Glycoaldehyde is further metabolized, first to glycolate, then glyoxylate, then finally to oxalate. Oxalate can bind to calcium to form calcium oxalate. It is not the ethylene glycol, but instead the intermediate metabolites that are toxic. Patients can present with impaired consciousness, seizures, and ophthalmoplegias. Hematuria, flank pain, and acute tubular necro-

sis appear over the following 24 hours. Oliguric renal failure, cerebral edema, cardiovascular collapse, non-cardiogenic edema, and myocarditis can develop over the next 48 hours. Treatment with either ethanol or fomepizole should be initiated immediately. Sodium bicarbonate should be used to treat severe acidosis. If ethylene glycol levels are elevated or if severe acidosis is present dialysis should be initiated. When treatment is successful, normal renal function is usually restored in 7-10 days, although permanent impairment has been reported. Documented ethylene glycol concentrations greater than 20mg per dL require treatment. However, obtaining timely levels is not always immediately available as very few laboratories can perform this assay. In an emergency, please contact your poison center for help in managing a case, and to determine emergent need for ethylene glycol levels.

Continued on page 8

TOXICOLOGY CROSSWORD PLANTS

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



Across

4. Plant exposures occur through contact, ingestion, or _____.
8. Toxic chemical found in antifreeze
9. Also known as inkberry, Indian polk, and red weed
10. Common name for *h.mantegazzianum sommier*

Down

1. Plant native to Europe, now found in upstate NY
2. Renal or _____ failure
3. Plant which causes Belladonna syndrome
5. Type of crystals found in urine with ethyleneglycol poisoning
6. Taste of antifreeze
7. Generic name for ethylene glycol antidote

Answers on page 6

SPI CORNER

ETHYLENE GLYCOL TOXICITY & ASSAY

Continued from page 7

In New York State, there are two official laboratories able to provide timely ethylene glycol levels;

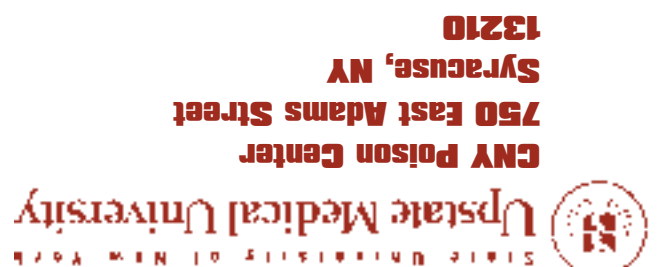
The Regional Toxicology Laboratory at Strong Memorial Hospital (Rochester, NY) has made available a new assay for ethylene glycol based on gas chromatography-mass spectrometry (GC-MS) and is specific for ethylene glycol. The previous enzymatic assay was not specific and is no longer available. The assay also determines the concentration of glycolic acid in the specimen. Therefore, the report of the ethylene glycol test will consist of ethylene glycol and glycolic acid concentrations in mg/dL units. Analysis is available from 0700-1530 daily. The specimen should be between 0.25 and 0.5 ml of blood in an SST or red top tube. The assay will detect ethylene glycol levels down to 1mg/dL and glycolic acid levels down to 2mg/dL. For further information contact Client Services for the laboratory at 585-275-8181 or your local poison center at 1-800-222-1222.

The Regional Toxicology Laboratory at the Albany Medical Center continues to provide 24 hour X 7 day per week availability for analysis of ethylene glycol based on gas chromatography-flame ionization detection. Other glycols, including diethylene glycol and propylene glycol, may also be detected in the analysis. For 24 hour test service, contact the Albany Medical

Center Stat Laboratory at 518-262-3515 or your local poison center at 1-800-222-1222. The Albany Medical Center laboratory recommends collection of blood in a 7 milliliter red top tube without anticoagulant or serum separator gel as soon as possible after the ingestion. Transportation must be arranged by the requesting facility. In cases where testing for other glycols or ethylene glycol derivatives are needed, please contact the laboratory director at Albany Medical Center (518-262-3515).

The Regional Toxicology Laboratory at Women and Childrens Hospital of Buffalo provide 24 hour X 7 day per week availability for analysis via an enzymatic method. We ask for a 3 ml sealed red-top vacutainer collection and delivered to the laboratory immediately after collection. A report will be available within one hour upon receiving the sample. For administrative information, please contact Kaleidahealth. Org. at WCHOB's Regional Toxicology Laboratory (716-878-7403).

The New York City Poison Center has limited support to provide ethylene glycol levels via gas chromatography for hospitals in the City of New York. For further information contact your local poison center at 1-800-222-1222.





TOXICOLOGY

A Quarterly Publication • Vol. X No. 3

LETTER

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 • <http://wnypoison.org>

**Ruth A. Lawrence Poison and Drug Information Center
Serving the Finger Lakes Region (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: 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 Ninth Annual Toxicology Teaching Day to be held on November 2, 2005 at the Sheraton Hotel and Conference Center in Syracuse. More information to come.

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

LI: Substance Abuse in the Emergency Department

Date: Tuesday, September 27, 2005.

Speaker: Dr Mark Su MD, State University of New York-Downstate Medical Center/Kings County Hospital, Brooklyn, NY • Assistant Professor of Emergency Medicine, Director of Medical Toxicology

Times: 12:15 PM-1:45 PM

Location: New Life Conference Rooms B&C, Winthrop-University Hospital, 259 First Street, Mineola, Long Island, New York 11501. Pre-Registration is required. Please contact *Denis Jao* at 516-663-2650 if interested in attending. Both Telephone and Televideo broadcasts will be available.

Please call administrative telephone numbers for more information.

Tox Trivia • •

1. A study of twenty-five deaths caused by poisoning among active and former major league baseball players between the years 1889-1990 cited what poison or toxin was the most frequent cause of demise in these players?
2. In 1992, the L.A. Gear company began production of high-tech sneakers with colored lights that flashed when the heels hit the ground! Some states considered these shoes a potential pollution hazard when disposed because of what toxic material in the lighting mechanism?
3. From 1985 to 1994, there were nineteen plant-related ingestion deaths reported to the national database of Poison Centers (AAPCC). Seven (36.8%) of the cases involved the ingestion of what specie of toxic plant?
4. This island still has "Bootlegger's Alley," a secluded beach used to drop off illegal liquor during prohibition on Long Island?
5. In Shakespeare's tragedy, Hamlet, the King who was Hamlet's father is murdered at the hands of a prisoner hired by the King's own brother. How did the killer administer the poison to his unfortunate victim?

NYPC Tidbits • •

1. What type of poisoning are you suffering from if you experience the "dry ice phenomenon" (where hot seems cold, and vice versa)?
A. Tetraodan
B. Ciguatera
C. Scombroid
D. Minamata
2. From what poisonous plant is the drug atropine obtained?
A. Wisteria
B. Foxglove
C. Oleander
D. Poison Ivy
E. Belladonna
3. This common plant is known to cause terrible hallucinations.
A. Dandelion
B. Bluebonnet
C. Crab grass
D. Jimson weed
E. Azalea

Answers:
Tox Trivia: 1. Carbon monoxide in 35% of the deaths; 2. Mercury; 3. The Hemlock species: Cicuta (water hemlock) and Conium (poison hemlock); 4. Shelter Island; 5. The poison, Henbane, was poured into the King's ear.

NYPC Tidbits: 1. B; 2. E; 3. D

Zometa (zoledronic acid)

Aredia (pamidronate disodium)

Novartis and FDA notified dental healthcare professionals of revisions to the prescribing information to describe the occurrence of osteonecrosis of the jaw (ONJ) observed in cancer patients receiving treatment with intravenous bisphosphonates, Aredia (pamidronate disodium) and Zometa (zoledronic acid). *May 05, 2005*

Counterfeit Drugs Purchased in Mexico

The FDA warned the public about the sale of counterfeit versions of Lipitor, Viagra, and an unapproved product promoted as "generic Evista" to U.S. consumers at pharmacies in Mexican border towns. The "generic Evista" was analyzed by FDA in coordination with the National Association of Boards of Pharmacy and was found to contain no active ingredient. The counterfeit Lipitor and counterfeit Viagra were analyzed by Pfizer, Inc. and were also found to contain no active ingredient. Consumers who have any of these counterfeit products should not use them and should contact their healthcare provider immediately. *May 10, 2005*

Famotidine Injection, 20 mg/2 mL

Bedford Laboratories and FDA notified healthcare professionals of the voluntary recall of one lot of Famotidine Injection, 20 mg/2 mL (NDC 55390-029-10), Lot# 609336, exp. 04/06, due to a lack of sterility assurance. *April 29, 2005*

Xigris [drotrecogin alfa (activated)]

Eli Lilly and FDA notified healthcare professionals of the stopping of enrollment in a randomized, double-blind, placebo-controlled trial of Xigris in pediatric patients with severe sepsis. Xigris is not indicated for use in pediatric severe sepsis. A planned interim analysis showed that Xigris was highly unlikely to show an improvement over placebo in the primary endpoint of "Composite Time to Complete Organ Failure Resolution" over 14 days. A numerical increase in the rate of central nervous system (CNS) bleeding in the Xigris versus the placebo group was also noted. Over the infusion period the number of patients experiencing an intracranial hemorrhage event was 4 versus 1 for the overall population (Xigris vs. placebo), with 3 of the 4 events in the Xigris group occurring in patients aged 60 days or less. *April 21, 2005*

Neurontin (gabapentin)

Pfizer Inc. and FDA notified healthcare professionals of the voluntary recall of one lot (40,000 bottles) of 100 mg capsules of its epilepsy medication, Neurontin, after a manufacturing mechanical failure resulted in some bottles containing empty or partially filled capsules. *April 22, 2005*

Betaseron (interferon beta-1b)

Berlex, Inc. reminded healthcare professionals of the prescribing information for Betaseron (interferon beta-1b) as it pertains to hepatic toxicity. Betaseron is approved for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. There have been reports during post-marketing safety surveillance of serious hepatic injury including autoimmune hepatitis and severe liver damage leading to hepatic failure and transplant. *April 15, 2005*

Trileptal (oxcarbazepine) Tablets and Oral Solution

Novartis Pharmaceuticals and FDA notified healthcare professionals about revisions to the WARNINGS and PRECAUTIONS sections of the prescribing information for TRILEPTAL (oxcarbazepine) tablets and oral suspension, indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and children ages 4-16 years with epilepsy. The updated WARNINGS section describes serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that have been reported in both children and adults in association with Trileptal use. *April 18, 2005*

Atypical Antipsychotic Drugs

The Food and Drug Administration has issued a public health advisory to alert health care providers, patients, and patient caregivers to new safety information concerning an unapproved, "off-label" use of certain antipsychotic drugs approved for the treatment of schizophrenia and mania. FDA has determined that the treatment of behavioral disorders in elderly patients with dementia with atypical (second generation) antipsychotic medications is associated with increased mortality. Clinical studies of these drugs in this population have shown a higher death rate associated with their use compared to patients receiving a placebo. *April 11, 2005*

COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

After concluding that the overall risk versus benefit profile is unfavorable, FDA has requested Pfizer, Inc. to voluntarily withdraw Bextra (valdecoxib) from the market. This request is based on: The lack of adequate data on the cardiovascular safety of long-term use of Bextra, along with the increased risk of adverse cardiovascular (CV) events in short-term coronary artery bypass surgery (CABG) trials that FDA believes may be relevant to chronic use. Reports of serious and potentially life-threatening skin reactions, including deaths, in patients using Bextra. The risk of these reactions in individual patients is

Continued on page 3

unpredictable, oc- of sulfa allergy, and after both short- and long-term use. Lack of any demonstrated advantages for Bextra compared with other NSAIDs. FDA is also asking manufacturers of all marketed prescription NSAIDs, for their products to include a boxed warning and a Medication Guide. The boxed warning will highlight the potential for increased risk of CV events with these drugs and the well-described, serious, and potentially life-threatening gastrointestinal (GI) bleeding associated with their use. The Medication Guide will accompany every prescription NSAID at the time it is dispensed to better inform patients about the CV and GI risks. Finally, FDA is asking manufacturers of non-prescription (OTC) NSAIDs to revise their labeling to include more specific information about the potential GI and CV risks, and information to assist consumers in the safe use of the drug. *April 07, 2005*

Reminyl (galantamine hydrobromide)

Ortho-McNeil Neurologics modified the PRECAUTIONS section of the Prescribing Information for Reminyl, approved only for the treatment of mild to moderate Alzheimer's Disease. The changes provide new safety information regarding the results of two randomized, placebo-controlled trials of 2 years duration in subjects with mild cognitive impairment (MCI). A total of 13 subjects on REMINYL (n=1026) and 1 subject on placebo (n=1022) died. The deaths were due to various causes which could be expected in an elderly population. About half of the REMINYL deaths appeared to result from various vascular causes (myocardial infarction, stroke), and sudden death. *March 31, 2005*

Zometa (zoledronic acid)

Novartis and FDA notified healthcare professionals of revisions to the DOSAGE AND ADMINISTRATION and WARNINGS sections of the prescribing information to reflect new safety information on management of patients with advanced cancer and renal impairment, whose baseline creatinine clearance is 60 ml/min or lower. The recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are provided in a table. It is recommended that, during treatment, serum creatinine be measured before each dose and treatment should be withheld for renal deterioration. *December 20, 2004*

Trecator (ethionamide tablets, USP) Tablets

Wyeth Pharmaceuticals announced that Trecator-SC (ethionamide tablets, USP) Sugar-Coated Tablets have been reformulated to film-coated tablets and renamed Trecator. The new film-coated tablet is more rapidly absorbed, resulting in higher peak concentrations (C_{max}) of ethionamide, which may potentially lead to patient intol-

erance when introduced at the same initial dose as the old sugar-coated tablet. *March 10, 2004*

PharMEDium Services Magnesium Sulfate 1 gram in 50mL D5W (piggyback) IV solution

FDA and PharMEDium Services of Houston notified healthcare professionals of the withdrawal of one lot of PharMEDium Services Magnesium Sulfate 1 gram in 50mL D5W (piggyback) IV solution, which may be contaminated with *Serratia marcescens* bacteria that can cause serious, life-threatening illness in patients with compromised immune systems. *April 8, 2005*

Xigris [drotrecogin alfa (activated)]

Eli Lilly and FDA notified healthcare professionals about revisions to the WARNINGS section of labeling for Xigris [drotrecogin alfa (activated)], a biological therapeutic product indicated for the treatment of adult patients with severe sepsis who are at high risk of death. This warning is based upon analyses of two clinical trial databases. Among patients with single organ dysfunction and recent surgery, all-cause mortality was numerically higher in the Xigris group compared to the placebo group. Patients with single organ dysfunction and recent surgery may not be at high risk of death and therefore may not be among the indicated population. *March 2005*

Avonex (interferon beta-1a)

FDA and Biogen notified healthcare professionals of revisions to the WARNINGS, PRECAUTIONS/Drug Interactions and ADVERSE REACTIONS/Post-Marketing Experience sections and Medication Guide. Severe hepatic injury, including cases of hepatic failure, has been reported in patients taking Avonex. Asymptomatic elevation of hepatic transaminases has also been reported, and in some patients has recurred upon rechallenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. *March 2005*

Elidel (pimecrolimus)

Protopic (tacrolimus)

The FDA issued a public health advisory to inform healthcare providers and patients about a potential cancer risk from use of Elidel (pimecrolimus) and Protopic (tacrolimus), products that are applied to the skin. This concern is based on information from animal studies, case reports in a small number of patients, and how these drugs work. It may take human studies of ten years or longer to determine if use of Elidel or Protopic is linked to cancer. In the meantime, this risk is uncertain and FDA advises that Elidel and Protopic should be used only as labeled, for patients who have failed treatment with other therapies. *March 10, 2005*

A Comatose Patient With A Mixed Overdose

Case Report:

Contributed By: Helen Koskinaris, Pharm D Candidate, St John's University, Tom Caraccio, Pharm.D., DABAT, Randi Mestel, RN, CSPI. Long Island Poison and Drug Information Center

PK is a 41 year-old male who was found unresponsive by his wife with several empty bottles of beer and the following medications by his side: Prozac® 10mg, Luvox® 25mg, Lexapro® 5mg and Percocet®. Upon presentation to a local emergency department (ED), he was reported to be comatose with the following vital signs: blood pressure of 194/107 mmHg, heart rate of 120 beats per minute, and respiratory rate of 6 per minute.

What Initial Measures should be considered?

Initial assessment of all medical emergencies follows the principles of basic and advanced cardiac life support. The adequacy of the patient's airway, degree of ventilation and circulatory status should be determined. Vital functions should be established and maintained. Vital signs, such as core body temperature, respiratory rate, and depth and air exchange, should be measured frequently. If the patient is comatose, management requires administering intravenous glucose, thiamine, and if hypoventilating, naloxone. Endotracheal intubation should also be considered to protect the airway. For all intentional ingestions, determination of the acetaminophen plasma concentration should be done 4 hours or more after ingestion.

What were the laboratory results for PK?

His electrolytes and a complete blood count were reported within normal limits except for a low potassium of 3.3 mEq/L and an elevated glucose level of 136 mg/dL. The acetaminophen level was reported as 12.2 µg/mL at unknown time of ingestion with normal liver function tests and the ethanol blood concentration was elevated at 173 mg/dL. The urine toxicity screen for common substances of abuse was reported as negative for benzodiazepines, barbiturates, opioids, cocaine, amphetamines and phencyclidine.

What Initial Measures for PK were performed?

In the ED the patient was given 4 mg of intravenous naloxone (Narcan®) and an amp of 50% dextrose without a response. This was followed by endotracheal intubation and placing the patient on assisted ventilation. His vital signs were measured at frequent intervals.

What type of drugs were found near this patient and how toxic could they be?

Fluoxetine (Prozac®) is a selective serotonin reuptake inhibitor (SSRI) antidepressant. It has been used for treatment of major depressive disorder, binge-eating and vomiting in patients with moderate-to-severe bulimia nervosa, obsessive-compulsive disorder (OCD), premenstrual dysphoric disorder and panic disorder. Fluoxetine is a second-generation antidepressant agent, which is a specific inhibitor of serotonin reuptake and does not effect the reuptake of norepinephrine or dopamine. It is available in 10, 20, 40 mg capsules and a 90 mg delayed release capsule; tablets of 10,

20 mg and an oral liquid of 20mg/5 ml.

The therapeutic dose usually ranges from 20-80 mg/day. Peak levels occur in 4 to 6 hours after oral administration and it is metabolized to an active metabolite, norfluoxetine. The half-life of fluoxetine is quite long (range of 1 to 4 days) and the metabolite can have a half-life of up to 16 days. Ingestions of 40 to 800 mg have produced minimal toxicity in adults. Common clinical effects after overdose include blurred vision, vomiting, lethargy, dizziness, insomnia, diarrhea, tremors, and abdominal pain. Seizures and significant cardiovascular toxicity and the development of serotonin syndrome (SS) is rare. The estimated human lethal dose of fluoxetine is 1,200 to 2,000mg.

Fluvoxamine (Luvox®) is a second selective serotonin reuptake inhibitor antidepressant used for the treatment of obsessive compulsive disorders. It is available in 25, 50 and 100mg tablets. The therapeutic dose range is 50 to 300 mg per day. Peak levels occur in 5 hours and the drug is metabolized to inactive metabolites. The half-life is about 15 hours. Patients have survived exposures with doses up to 6.5 grams. Coma has been reported in overdoses of 1.5 and 3 grams. Effects after overdose are similar to fluoxetine.

Escitalopram (Lexapro®) is a serotonin reuptake inhibitor antidepressant that this patient took used for the treatment of depression and generalized anxiety disorder. Escitalopram is the S-enantiomer of citalopram and is available in 5, 10 and 20 mg tablets and an oral solution of 1 mg/ml. The therapeutic dose range is 10-20mg/day orally. Peak levels occur in 4-6 hours for the parent drug. Escitalopram is metabolized by the liver via CYP2C19 and 3A4 to an active metabolite, S-desmethylcitalopram. The half life of the parent drug is 27-32 hours and 59 hours for its metabolite. Toxicity is thought to be similar to citalopram (Celexa®). Seizures are reported following overdoses which have exceeded 600 mg of citalopram and several reports of overdose with citalopram have resulted in death following doses greater than 2,000 mg (Grundemar et al, 1997). Unique toxic effects have included seizures, and prolongation of the QTc interval (Personne et al, 1997). Patients should be monitored for a 24 hour period.

(Percocet®) is a narcotic analgesic combination which contains acetaminophen and oxycodone. Acetaminophen is used primarily for its antipyretic and analgesic effects, which are mediated via the central nervous system. Oxycodone is an opioid which stimulates the mu and kappa subtypes of the opiate receptor, thereby causing analgesia. Percocet® is available in several different strengths of acetaminophen from 325-650 mg and oxycodone in concentrations of 2.5-10mg. The total daily therapeutic dose should not exceed 4,000 mg of acetaminophen and 60 mg of oxycodone. Ingestion of acetaminophen in an acute overdose of greater than 150mg/kg or 7.5g has caused liver injury. In acetaminophen overdose, the glucuronidation and sulfation

Continued on page 5

pathways become saturated which increases P450 mediated production of the highly reactive metabolite, N-acetyl-p-benzoquinoneimine (NAPQI). This exhausts the natural protective stores of cellular glutathione resulting in cell death and zone 3 (centrilobular or distal acinar) degeneration of the liver.

What are the different phases of Acetaminophen Toxicity?

There are four phases of the intoxication usually described for acetaminophen intoxication. Remember that the clinical course may overlap and the absence of a phase does not exclude toxicity. Phase I occurs within 0.5 to 24 hours after ingestion and may consist of a few hours of malaise, diaphoresis, nausea, and vomiting or produce no symptoms. CNS depression or coma is usually not seen in this phase unless an extremely high level has been reported. Phase II occurs 24 to 48 hours after ingestion and is a period of diminished symptoms. The liver enzymes AST (earliest), and ALT may increase as early as 4 hours or as late as 36 hours after ingestion. Phase III occurs 48 to 96 hours after ingestion with peak liver function abnormalities at 72-96 hours. The degree of elevation of the hepatic enzymes does not correlate with outcome. Recovery starts about 4 days unless hepatic failure develops. Less than 1% of patients develop fulminant hepatotoxicity. Phase IV occurs 4 to 14 days after ingestion with hepatic enzyme abnormalities reaching resolution. If extensive liver damage has occurred, sepsis and disseminated intravascular coagulation may ensue. Death can occur at 7-14 days. Transient renal failure may develop at 5-7 days with or without evidence of hepatic damage. Rare cases of myocarditis and pancreatitis have been reported.

How toxic is Oxycodone?

Oxycodone acts to depress the central nervous system and may produce coma, cessation of respiration and miosis. Ingestions of opioids in doses greater than 1 mg/kg have produced mild to moderate symptoms of CNS depression in 51% of children in 30 to 60 minutes. Although the lethal dose of oxycodone is unknown, the estimated lethal dose for codeine in adults is 7 to 14 mg/kg. Addiction following chronic usage of oxycodone is common and results in a withdrawal state upon termination.

How toxic is Beer?

Beer can contain ethanol in concentrations of 2.5% to 6%. Ethanol is the most common psychoactive drug used by children and adolescents in the United States, and it is one of the most commonly abused drugs in the world. Ethanol is a GABAergic central nervous system depressant. It promotes cutaneous vasodilation (contributing to hypothermia), stimulates secretion of gastric juice (potentially causing gastritis), inhibits secretion of antidiuretic hormone, inhibits gluconeogenesis (potentially causing hypoglycemia), and influences fat metabolism (potentially causing lipidemia). The concentration of ethanol peaks 30-60 minutes after ingestion. The co-ingestion of food also slows absorption. Ethanol is primarily metabolized in the liver. Approximately 90% of an ethanol load is broken down in the liver to acetaldehyde and ultimately carbon dioxide and water; the remainder is eliminated as the parent drug by the

kidneys and lungs. The toxic dose is 1 mL/kg of absolute or 100% ethanol or 200-proof ethanol (proof defines alcohol concentration in beverages) results in a blood concentration of 100 mg/dL. Children are considered more sensitive to the effects of ethanol compared to adults. The potentially fatal dose is 3 g/kg for children vs 6 g/kg for adults. Children frequently develop hypoglycemia at a blood level greater than 50 mg/dL. The clinical effects following an acute exposure are dose related and can include CNS depression (narcosis, coma, respiratory failure, death), hypothermia, acidosis, hypoglycemia, hypotension, GI upset/bleed, dysrhythmias, aspiration and electrolyte imbalances. Chronic exposure can produce physical dependence. CNS effects (amnesia, dementia, somnolence), cardiomyopathy, hepatotoxicity, pancreatitis and GI bleeding may be associated with chronic abuse.

What is the role of Gastrointestinal decontamination for the drugs taken by this patient?

Gastrointestinal decontamination can be carried out by administering activated charcoal if the patient presents awake and alert with a history of a toxic dose of fluoxetine, fluvoxamine, escitalopram, acetaminophen/oxycodone within 1 hour post ingestion. Ethanol does not readily adhere to activated charcoal. The activated charcoal can be given as a slurry (240 mL water/30 g charcoal). The usual dose is 25 to 100 g in adults/adolescents, 25 to 50g in children (1 to 12 years old), and 1g/kg in infants less than 1 year old.

How do you treat seizures from these drugs?

If seizures occur, administer IV benzodiazepines such as lorazepam (dose for an adult is 2 to 4mg; dose for a child is 0.05 to 0.01 mg/kg) or diazepam (dose for an adult: is 5 to 10mg), which can be repeated if necessary.

How should hypotension be managed?

Place the patient in the trendelenburg position and administer 10 to 20 ml/kg of 0.9% saline as a bolus. Further fluid therapy should be guided by central venous pressure or right heart catheterization to avoid volume overload. Pressor agents such as intravenous norepinephrine, 0.1 to 0.2 microgram/kg/minute can be used to maintain adequate blood pressure.

How should other cardiac complications be treated?

For a **wide QRS complex**, IV sodium bicarbonate administration in a dosage of 1 to 2 mEq/kg can be given as needed to maintain a serum pH 7.45-7.55. Monitor ECG, serum electrolytes and arterial blood gases carefully.

Torsades de pointes may occur from drugs such as escitalopram. In hemodynamically unstable patients, electrical cardioversion may be indicated. Torsades de pointes in stable patients can be treated with either magnesium sulfate, isoproterenol, and/or atrial overdrive pacing. Magnesium sulfate can be administered in a dose for adults consisting of 2 g IV over 1 to 2 minutes. It can be repeated as a 2 g bolus and an infusion of 0.5 to 1g/hr can be given if

dysrhythmias recur. The dose for children is 25 to 50 mg/kg given as an IV infusion over 5 to 15 minutes. Isoproterenol is a less desirable as an alternative because of the vasodilation effects that can be produced.

In an overdose, an ECG should be obtained in symptomatic patients, and monitor for evidence of serotonin syndrome which can be induced by the SSRI's.

How should the **SEROTONIN SYNDROME** be managed?

Patients can be managed by discontinuing the serotonergic drug therapy and using supportive care. Careful attention to decreasing excessive muscle activity and thereby decreasing incidence of hyperthermia is critical. Benzodiazepines are useful for excessive muscle activity, however, non-depolarizing paralytics may be used in severe cases. For mild/moderate asymptomatic hypertension, pharmacologic intervention is usually not necessary. For hypertensive emergencies, nitroprusside is preferred. 0.1 to 5 microgram/kg/minute IV infusion; up to 10 micrograms/kg/minute may be required.

Cyproheptidine (Periactin®) (4-8 mg orally initially and repeated every 4 hours) can help block the action of serotonin and may counteract SS symptoms. The syndrome tends to resolve within 24 hours but it may last for days if the half-life of the interacting drugs are prolonged. Monitor the vital signs and EEG, creatine kinase and urine for myoglobinuria if symptomatic. Use fluids to maintain a urine output of >3 mL/kg/hour if there is risk of myoglobinuria producing renal failure. If systemic acidosis or urine pH <6 and myoglobinuria is present alkalinize the urine with sodium bicarbonate.

What specific antidotes can be used for an acetaminophen/oxycodone overdose?

Naloxone (Narcan®) can be administered in a suspected overdose of an opioid drug. The adult and pediatric dose is 0.4 to 2mg IV, repeated as needed to reverse the signs and symptoms of respiratory depression.

N-acetylcysteine (NAC, Mucomyst®, Acetadote®):

NAC is the recommended treatment for acetaminophen (APAP) poisoning because of several beneficial effects including generation of glutathione, enhancing non-toxic routes of acetaminophen metabolism, detoxifying N-acetyl-p-benzoquinonimine, and free radical scavenging. If an APAP level is in the potentially toxic range on the nomogram or if a toxic amount has been ingested (7.5 grams or more), NAC therapy should be started, preferably within 8 hours of ingestion.

How can NAC be given?

The **oral loading dose** is 140mg/kg as a 5% solution in a soft drink or juice. The oral maintenance dose is 70mg/kg orally as a 5% solution in a soft drink or juice every 4 hours. If the patient vomits or is unable to take the oral form of NAC, there is an IV preparation available called Acetadote (R). The recommended **IV dose** regimen for acetaminophen poisoning is a loading dose of 150 mg/kg in 200mL of 5% dextrose over 30 minutes followed by a first maintenance dose of 50 mg/kg in 500mL of 5% dextrose over 4 hours;

and a second maintenance dose of 100 mg/kg in 1000mL of 5% dextrose over 16 hours. The volume of diluent should be altered in young pediatric patients. Although Acetadote (R) should be administered 8 to 10 hours after ingestion of a potentially hepatotoxic dose of acetaminophen, it can still be effective if given after this time frame.

What is the management for Ethanol intoxication?

Treatment includes supportive care. The patient should be positioned to prevent aspiration. Thiamine, glucose, and naloxone, should be considered. Airway Management- Intubate if clinically indicated for airway protection or ventilatory support. Fluid/Electrolyte Balance Regulation- An IV line should be started. Hydrate with 0.9% NaCl with 5% dextrose as clinically indicated. Dextrose is indicated if the bedside glucose level is less than 60 mg/dL.

Comments and Pearls

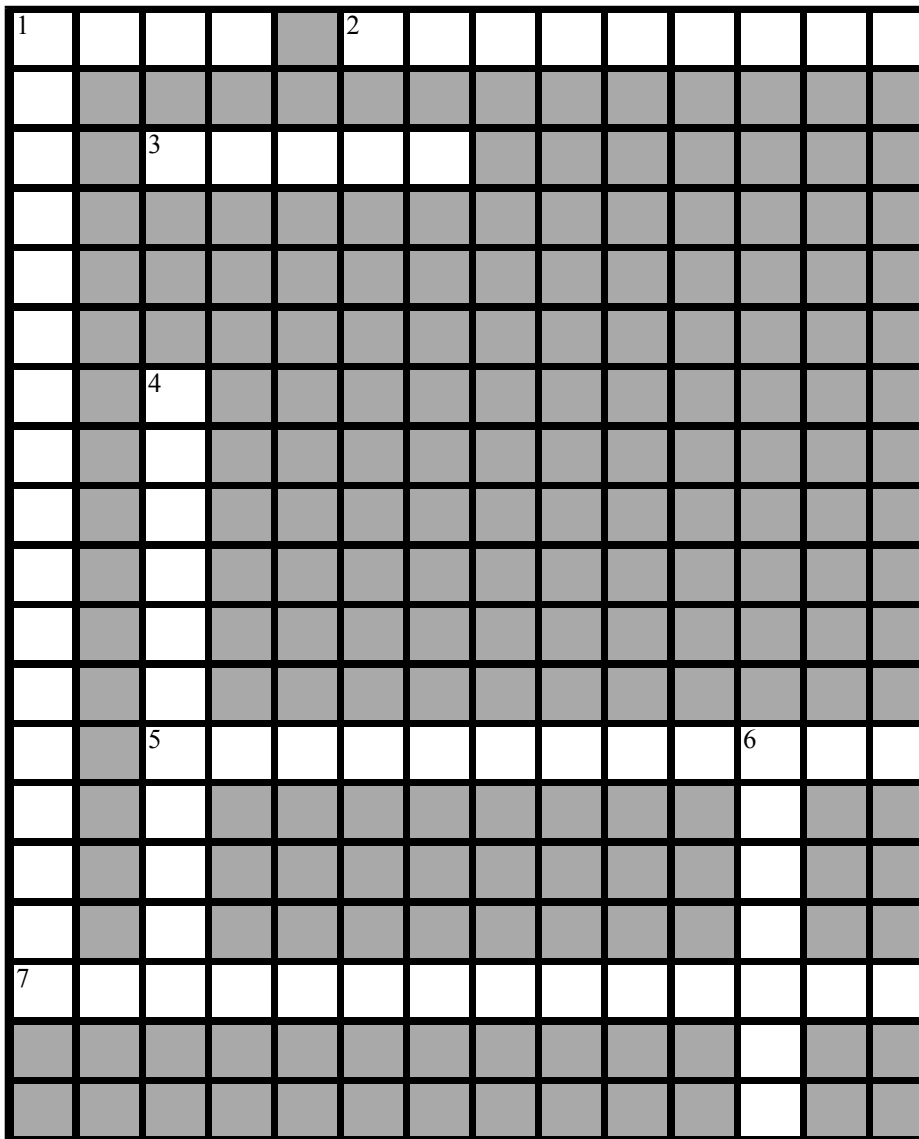
1. In 2004 the FDA issued a Public Health Advisory warning that all the SSRI can increase the risk of suicidality (thinking and behavior) in children and adolescents. A black box warning about this is now required to be in the package insert for all of the SSRI's regarding this concern.
2. For SSRI like fluoxetine, remember that they should not be used in combination with a non-selective MAO inhibitor such as isocarboxazid (Marplan®) or phenelzine (Nardil®), because of a potentially fatal interaction. At least 5 weeks should elapse between discontinuation of an SSRI and initiation of treatment with an MAO inhibitor and 14 days between the discontinuation of an MAO inhibitor and the initiation of treatment with an SSRI.
5. The **adverse event** most commonly associated with IV NAC administration is an anaphylactoid reaction including rash, wheezing, itching and in some cases hypotension. These reactions are dose related and therefore are most common with the loading dose. The frequency of adverse events has been reported to be between 0.2% and 20.8%. Anaphylactoid reactions associated with IV NAC are thought to be non-immunologic and perhaps caused by histamine release, according to dose response and rapidity of reaction in patients not previously exposed to the drug.

What was the Outcome of the case?

The following morning the patient was admitted to the ICU. He remained intubated and sedated. He was on assist control and breathing over the vent at a rate of 10-16. His heart rate was 70s to 90s bpm, blood pressure was 100/50mmHg. IV Fluids were given (0.9% saline at a rate of 100 mL/hour). Thiamine IV was given. The patient was to be continued to be observed. NAC was given until the APAP level was negative and the liver function tests remained normal. Later that same day, the patient was extubated. Respirations were within normal limits. His vitals were recorded as stable. The patient was described as awake and alert. The patient continued to be observed and was going to be transferred out the next day, after psyche evaluation. All laboratory tests were reported within normal limits.

TOXICOLOGY CROSSWORD DRUGS

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



Across

1. What class of drugs does Fluoxetine (Prozac®) belong to?
2. The toxicity of Escitalopram (Lexapro®) is similar to which agent?
3. What is the longest number of days it usually takes for renal toxicity to develop in acetaminophen intoxication?
5. What is a serious effect produced by ethanol intoxication in children?
7. Which test should be monitored for 24 hours in a Escitalopram overdose?

Down

1. What syndrome has been associated with an excessive amount of Escitalopram?
4. What is the name of the key substrate that becomes depleted in acetaminophen overdose?
6. Name a clinical effect produced by an oxycodone overdose?



SPI CORNER TOPIC: **MORNING GLORY**

Contributed by: William Gaffney, MS, Tom Caraccio, Pharm.D., DABAT, Randi Mestel, RN, CSPI, Long Island Poison and Drug Information Center

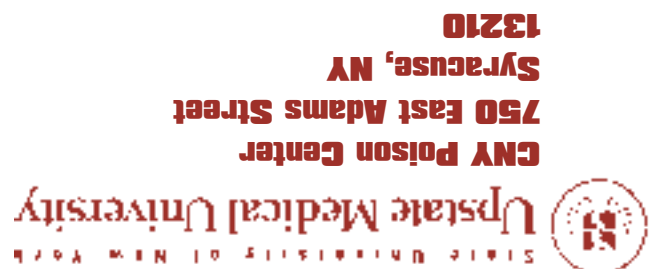
An article entitled "Seeds of Destruction" recently appeared in a Long Island newspaper following the hospitalization of a local teenager who experimented with the ingestion of Morning Glory seeds. The reporter examined an alarming incident which exposed the ease of access which young adults have to this hallucinogen. The teenager had a reaction to the "trip" he likely won't soon forget. According to a friend, the youngster and another friend decided to try the seeds because they had "heard it was like LSD," and "it was available without having problems with the law." While the teen's "trip" began during the weekend, he continued to react to the drug as he began his week at school and was soon admitted to a local hospital.

Upon being admitted to the hospital the Poison Center was consulted regarding this case. The real incidence of the abuse of these seeds by teenagers isn't known. The morning glory seeds are a known hallucinogen containing alkaloids that are similar to LSD.

Consumption of these seeds was popularized in the 1960s by teenagers and young adults who ingested the seeds for their hallucinogenic properties. Common street names include *Heavenly Blue*, *Blue Star* and *Flying Saucers*. The seeds must be chewed for absorption of the alkaloids to occur. Restlessness, increased awareness and socialization followed by relaxation for several hours are typical effects

reported with ingestions of 20-40 seeds. A dose of 100-150 seeds has produced effects similar to ingestion of 75-150 ug/kg of LSD. This amount has been associated with spatial distortions, hallucinations, enhanced imagery and mood elevations for 1-4 days. Ingestions of 200-250 seeds have produced additional effects of nausea, vomiting, abdominal pain, lethargy and paresthesias. In a case reported in the literature, a 24-year old who took 300 seeds had effects which allegedly led the victim to commit suicide.

While the victim's friend stated that the consumption of drugs like morning glory seeds are not common and that only a small group of kids know about them, he also said that medications like Sudafed® or NyQuil® are used recreationally when there is nothing else going on. At least one local merchant has said young girls often come in and buy the seeds, and the merchant was not aware that the seeds could be harmful. Morning Glory is not a controlled plant in the United States. Live plants and seeds of any variety are legal to buy, sell or possess. Both plants and seeds are regularly sold by botanical supply companies. In some jurisdictions, Morning Glory (*ipomoea* species) is considered to be an invasive, unwanted weed plant and the control of growing the plant and distribution of the seeds fall under laws and regulations of weeds. In Arizona all *ipomoea* species are listed as "noxious weeds" and are illegal to cultivate.





October 2005

The NY State Poison Centers

TOXICOLOGY

A Quarterly Publication • Vol. X No. 4

LETTER

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 • <http://wnypoison.org>

**Ruth A. Lawrence Poison and Drug Information Center
Serving the Finger Lakes Region (FL)**

585.273.4155 • www.FingerLakesPoison.org

Upstate New York Poison Center (UNY)

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

Tox Trivia • •

1. The trade name of FDA approved intravenous NAC?
2. Where did our patient get exposed to diethylene glycol?
3. Can oral NAC be given intravenously?

NYPC Tidbits • •

1. This toxin was found in elixir of sulfanilamide and toxicity related led to the passage of the Food, Drug and Cosmetic Safety Act of 1938.
2. This toxic effect appears to be permanent after diethylene glycol poisoning.
3. Ethylene glycol levels will be positive after diethylene glycol exposure? (*True/False*)

Answers on page 7

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).

UNY: Please mark your calendars for our Ninth Annual Toxicology Teaching Day to be held on November 2, 2005 at the Sheraton Hotel and Conference Center in Syracuse. A brochure can be obtained by e-mailing fosterl@upstate.edu

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

LI: Pre-Registration is required. Please contact Mr. Denis Jao at 516-663-2650 to register.

Both Telephone and Televideo broadcasts will be available.

Target Audience: Physicians, Pharmacists, Nurses, Physician-Assistants, Laboratory technicians, EMS staff, medical/nursing/pharmacy students and other healthcare professionals.

Location: New Life Conference Rooms B&C
Winthrop-University Hospital
259 First Street

Mineola, Long Island, New York 11501

Times for ALL Conferences are: 12:15 PM-1:45 PM

LI (cont'd):

Tuesday, September 27, 2005: SUBSTANCE ABUSE

Mark Su, MD, ABMT, ABEM

Assistant Professor of Emergency Medicine

Director of Medical Toxicology

State University of New York - Downstate Medical Center/
Kings County Hospital, Brooklyn, NY

Monday, October 24, 2005: BETA BLOCKER

TOXICOLOGY: RECOGNITION AND MANAGEMENT

Gerold Brody, MD, ABEM

Chairman Ambulatory Medicine

Winthrop University Hospital

Mineola, NY

Tuesday, November 29, 2005: PERCUTANEOUS

ABSORPTION AND DISTRIBUTION OF METHANOL
IN A HOMICIDE

Joseph Avella, MS, Ph.D, FTS, ABFT

Forensic Scientist II

Sidney B Weinburg Center for Forensic Sciences

Hauppauge, NY

Please call administrative telephone numbers for more information.

Injectable Products made by Central Admixture Pharmacy Service (CAPS) of Lanham, Maryland

FDA is notifying healthcare professionals and hospitals about a product recall involving all injectable products manufactured by Central Admixture Pharmacy Services, Inc. of Lanham, Maryland (CAPS) due to concerns regarding the sterility of these injectable products. *September 17, 2005*

NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]) NovoLog (insulin aspart [rDNA origin] injection)

To facilitate the dispensing of the correct product, color branded labeling has been introduced for NovoLog Mix 70/30, a premixed insulin analog, and NovoLog, a rapid-acting insulin analog. *August 26, 2005*

Erbix (cetuximab)

The WARNINGS and DOSAGE AND ADMINISTRATION sections have been revised to notify healthcare providers about specific recommendations on observation periods following Erbix infusion. In addition, the PRECAUTIONS and ADVERSE REACTIONS sections have been revised to discuss results seen in Erbix clinical trials regarding an increased incidence of hypomagnesemia. *September 13, 2005*

Herceptin (trastuzumab)

Genentech and FDA notified healthcare professionals of updated cardiotoxicity information related to the use of Herceptin (trastuzumab), obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study (B-31), demonstrating a significant increase in cardiotoxicity in patients who were randomized to the Herceptin-containing arm as compared to patients who received chemotherapy alone. *August 2005*

Alcohol-Free Mouthwash and Hygiene Kits by Medline

Medline and FDA notified healthcare professionals about a nationwide recall of Alcohol-Free Mouthwash and Hygiene Kits containing mouthwash because of potential contamination with *Burkholderia cepacia*. *August 29, 2005*

Trypan Blue 0.06% Ophthalmic Solution

Custom RX Compounding Pharmacy and FDA notified ophthalmologists, other healthcare professionals, and consumers about a nationwide recall of Trypan Blue 0.06% Ophthalmic Solution, intended for use in the eyes during cataract surgery, because it may be contaminated with *Pseudomonas aeruginosa*. *August 26, 2005*

Isotretinoin - Accutane and generic isotretinoin

FDA notified healthcare professionals and patients of the approval of a strengthened risk management program for Accutane and generic isotretinoin. *August 12, 2005*

Perrigo Infants' Oral Drops Containing Enclosed Syringe

Perrigo and FDA notified healthcare professionals and consumers of the recall of all lots of concentrated infants' drops that are packaged with a dosing syringe bearing only a "1.6 mL" mark containing: acetaminophen, acetaminophen, dextromethorphan HBr, and pseudoephedrine HCl, or dextromethorphan HBr, and pseudoephedrine HCl. *August 01, 2005*

Counterfeit "Lipitor" Sold in the United Kingdom

FDA alerted U.S. residents to the recent recall of a batch of counterfeit "Lipitor" (atorvastatin) sold in the United Kingdom (U.K.). *July 29, 2005*

Raptiva (efalizumab)

Healthcare professionals and patients were informed about reports of immune-mediated hemolytic anemia and warnings regarding postmarketing reports of thrombocytopenia and serious infections including necrotizing fasciitis, tuberculous pneumonia, bacterial sepsis with seeding of distant sites, severe pneumonia with neutropenia, and worsening of infection. *July 15, 2005*

Mifeprex (mifepristone)

Danco Laboratories and FDA have revised the BOXED WARNING and WARNINGS sections of the Prescribing Information, the Medication Guide and Patient Agreement to inform healthcare professionals of four cases of septic deaths in the United States in women following medical abortion with mifepristone (Mifeprex) and misoprostol. *July 19, 2005*

Natreacor (nesiritide)

Scios and FDA notified healthcare professionals about the recommendations of an expert panel of cardiology and heart failure clinicians with regard to NATRECOR (nesiritide). The panel provided a consensus statement an educational campaign to ensure that clinicians understand when the use of NATRECOR is appropriate and when it is not appropriate. *July 13, 2005*

Continued on page 3

Fentanyl Transdermal (Skin) Patch

FDA issued a public health advisory to alert health care professionals, patients and their caregivers of reports of death and other serious side effects from overdoses of fentanyl in patients using fentanyl transdermal (skin) patches for pain control. *July 15, 2005*

Palladone (hydromorphone hydrochloride)

FDA issued a public health advisory to notify health care professionals and consumers that the sponsor of Palladone, Purdue Pharma, has agreed to suspend sales and marketing of Palladone (hydromorphone hydrochloride, extended release capsules), a potent narcotic painkiller, because of the potential for severe side effects if Palladone is taken with alcohol. *July 13, 2005*

Duragesic (fentanyl transdermal system)

Janssen and FDA notified healthcare professionals of changes to the BOXED WARNING/WARNINGS, CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the prescribing information for Duragesic. *June 2005*

Cialis (Tadalafil)Levitra (Vardenafil hydrochloride)Viagra (Sildenafil citrate)

FDA notified healthcare professionals of updated labeling for Cialis, Levitra and Viagra to reflect a small number of post-marketing reports of sudden vision loss, attributed to NAION (non arteritic ischemic optic neuropathy).

Liqiang 4 Dietary Supplement Capsules

FDA notified consumers and healthcare professionals about the risks of taking Liqiang 4 Dietary Supplement Capsules because they contain glyburide – a drug that could have serious, life-threatening consequences in some people. *July 01, 2005*

Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications

FDA notified healthcare professionals about the availability of updated Healthcare Professional and Patient Information Sheets for antidepressant medications that were the subject of a June 30, 2005 Public Health Advisory issued about the risk of suicidality (suicidal thinking or behavior). *July 01, 2005*

Iressa (gefitinib)

AstraZeneca and FDA notified healthcare professionals of new approved labeling for Iressa that states the medicine should be used only in cancer patients who have already taken the medicine and whose doctor believes it is helping them. *June 17, 2005*



Quality Care Products L.L.C./Able Laboratories Inc. Drugs

Quality Care Products, LLC, a federally licensed drug re-packer, and FDA notified healthcare professionals of a nationwide recall because of the FDA's serious concerns that they were not produced according to quality assurance standards. *June 15, 2005*

COX-2 Selective (includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

FDA has requested that sponsors of all non-steroidal anti-inflammatory drugs (NSAID) make labeling changes to their products to include a boxed warning, highlighting the potential for increased risk of cardiovascular (CV) events and the well described, serious, potential life-threatening gastrointestinal (GI) bleeding associated with their use. *June 15, 2005.*

Children's Tylenol Meltaways - 80 Mg, Children's Tylenol Softchews - 80 Mg Jr. Tylenol Meltaways - 160 Mg

McNeil Specialty Pharmaceuticals and FDA notified consumers and healthcare professionals about a nationwide recall of all lots and all flavors of Children's TYLENOL Meltaways 80 mg, Children's TYLENOL SoftChews 80mg, and Junior TYLENOL Meltaways 160mg. The recall addresses issues regarding the design of the blister package, information on the package, and bottle cartons for the products that may be confusing and lead to improper dosing, including overdosing. *June 03, 2005.*

Diethylene Glycol and Neurologic Toxicity

Case Report:

Contributed by: Michael Holland, MD, Medical Consultant, Upstate New York Poison Center, Syracuse, NY

Case Report: A 27 year old male with past psychiatric problems and multiple prior overdoses, presented to the Emergency Department (ED) complaining of nausea and vomiting approximately 24 hours after ingesting 16 ounces of wallpaper stripper containing an unknown percentage of diethylene glycol. He had consumed it for its presumed intoxicating effects. Upon arrival, he was awake and alert with a normal physical and neurologic examination. His heart rate was 56 beats per minute, blood pressure 168/67 mmHg, respiratory rate 16 breaths per minute with 96 % oxygen saturation on room air. Initial laboratory studies revealed an increased anion gap metabolic acidosis of 20 (normal <12), with bicarbonate level of 17 mmol/L (normal: 22-30 mmol/L), acute renal failure with creatinine of 3.7 mg/dL (normal: 0.8-1.5 mg/dL) and blood urea nitrogen (BUN) of 19 mg/dL (normal: 9-20 mg/dL). Hepatic transaminases on the day of presentation were normal.

What is diethylene glycol, and how commonly is it used in consumer products? Diethylene glycol (DEG, CAS # 111-46-6) is prepared commercially through heating ethylene oxide with glycol, forming two ethylene glycol molecules joined by an ether bond. DEG is a colorless, nearly odorless, syrupy liquid with a sweet taste. It has a molecular weight of 106 Daltons, and is soluble in water, acetone and ether, but insoluble in benzene and toluene. Because of its cheap production costs and water and solvent solubility, it has seen widespread use in industrial processes as well as in consumer products. The myriad of uses of DEG include wallpaper strippers, Sterno® liquid fuel, glass cleaners, brake fluids, theatrical fog solutions, household tints and dyes, in waxes and adhesives as a freezing point depressor, and automotive antifreeze. This ready availability, along with variable warning labels and protective packaging has led to and an unacceptably high potential for future poisonings.

What is the historical significance of DEG poisoning?

The first experience with human poisoning occurred in the USA in 1937, when it was used as a diluent for elixir of sulfanilamide. The Massengil Company had tested the sulfanilamide, but not the DEG vehicle, as this was not required at that time. Severe poisoning resulted in the death of at least 105 people from renal failure. That tragedy has major historical significance for medical care in the USA, since it led to the passage of the Food, Drug and Cosmetic Safety Act of 1938, and greatly strengthened the regulatory powers of the FDA.

Several mass poisonings involving DEG ingestion as an accidental excipient in liquid medications have occurred since the US Massengil tragedy. Since liquid medications are produced for pediatric preparations, the overwhelming majority of victims were young children. DEG caused the death from acute renal failure of 85 children in Haiti when the glycerol diluent in an acetaminophen elixir was found to have been contaminated with DEG. DEG has no odor, and a pleasant, sweet taste, which affords no protection or warning for the unaware recipients of the contaminated medications. Similar disasters with DEG contamination of liquid medication diluents have also occurred in Argentina, India, Bangladesh, Nigeria, and South Africa.

What are the main toxicities of DEG?

In all the mass poisoning reports, the patients developed severe metabolic acidosis and renal failure. Since these historical mass poisonings either occurred prior to the availability of hemodialysis or in countries with limited availability of this intervention, early morbidity and mortality rates were quite high and despite use of peritoneal dialysis

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in some cases, most poisoned patients died from renal failure. Some of these reports mentioned neurological injuries as well, but it appears that most victims did not survive long enough for the more severe neurological abnormalities to become apparent. In these mass poisoning exposures, renal toxicity progressing to renal failure was a consistent finding, with neurologic symptoms infrequently reported.

Neurologic complications have been described in more recent reports from developed countries, though the mechanism remains unknown.

Initial presentation of patients consisted of gastrointestinal effects with significant vomiting and abdominal pains. Patients who were more significantly poisoned experienced subsequent hepatic and renal injury. In cases where hemodialysis was promptly instituted, patients survived only to develop neurological impairments of varying severity. Cranial neuropathies have been seen, as well as progressive, diffuse demyelinating sensori-motor polyneuropathy. Patients can have EEG evidence of severe encephalopathy as well, and in fact can remain unresponsive and completely paraplegic for weeks. At this stage, their clinical prognosis can appear dismal, and the question of whether to withdraw life support should not be treated lightly. Several reports have documented good neurologic recovery in some of these cases. Since these neurologic signs begin to manifest at 5- 10 days post-ingestion, most of the victims of the early epidemic poisonings such as those in India and Jamaica never survived long enough to manifest this aspect of DEG toxicity.

What are the toxicokinetics of DEG?

Animal studies indicate that DEG is well-absorbed after oral administration in both rats and dogs. Its volume of distribution appears to be approximately 0.8 L/kg. It was once believed that DEG metabolism involved initial cleavage into two molecules of ethylene glycol (EG), then subsequent metabolism into the toxic byproducts glycolic acid and oxalic acid. However, it is well-known that ether bonds are relatively stable and rarely undergo metabolic cleavage. More recent studies have documented that the urinary sediment from renal failure poisoning victims showed none of the expected oxalate crystals seen in patients similarly poisoned with EG. Toxicokinetic studies in animals have determined that alcohol dehydrogenase and aldehyde dehydrogenase produce the primary metabolite 2-hydroxyethoxyacetic acid (HEAA). In these test animals, more than 80% of the dose is excreted in the urine: over 50% as the unchanged parent compound, and approximately 10-30% as the HEAA metabolite.



What initial management options should be considered for this patient?

In addition to standard poison management, immediate concerns here should be the management of his metabolic acidosis and acute renal failure. This combination should prompt laboratory investigation for toxic alcohol, specifically ethylene glycol and DEG.

Are alcohol dehydrogenase inhibitors indicated in the management of DEG poisoning?

Since DEG is known to be metabolized into HEAA by ADH (alcohol dehydrogenase) and ALDH (aldehyde dehydrogenase), it is logical to assume that inhibition of its metabolism by ADH with either ethanol or fomepizole would prevent toxic metabolite formation. This has been shown in animal studies, and significantly reduced DEG toxicity in these animals. Although failure of this treatment has been reported by some authors, fomepizole has been used in conjunction with hemodialysis in two cases of DEG poisoning, both reporting a good outcome. However the case described by Brophy, et al had no clinical symptoms of toxicity, and the pre-dialysis serum level of DEG was only 1.7 mg/dL. Compared to known toxic levels of other toxic alcohols (methanol and ethylene glycol, toxic levels >25mg/dL), this low level may have simply represented an insignificant exposure, and presumably would have done well without any intervention. The case described by Borron et al had an anion gap acidosis and an osmolar gap at presentation, but no renal failure. Prompt hemodialysis was instituted as well as administration of fomepizole, and the patient did well.

Ethylene glycol (EG) ingestions can theoretically be managed with ADH inhibition alone, as long as acidosis has not developed and the patient's renal function remains normal. The parent EG molecule is not particularly toxic, and as long as production of the toxic metabolites is prevented, renal clearance of EG can occur. Although infrequently used in this country due to the cost of fomepizole, this management scheme is frequently utilized in other countries. However, the same scheme cannot be generalized to DEG poisoning. The parent DEG molecule itself may be directly nephrotoxic, in addition to the metabolites. Therefore, ADH inhibitors alone are not adequate treatment. All DEG ingestions with acidosis and/or renal failure should receive fomepizole and immediate referral for hemodialysis.

What is the role of hemodialysis in DEG ingestions?

Emergent hemodialysis is critically important for management of these cases. It appears from case reports that the parent molecule is potentially toxic, as well as the metabolites. As noted above, good results were achieved in case reports of fomepizole use in conjunction with hemodialysis. Hemodialysis is the only intervention that has allowed patients with renal failure associated with DEG poisoning to survive, as peritoneal dialysis was ineffective in the Haiti and India epidemics.

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In our case, hemodialysis was initiated shortly after presentation for renal failure and acidosis. Additionally, thiamine and pyridoxine were added. Quantitative analysis for ethanol, methanol, ethylene glycol and isopropyl alcohol were performed on the day of presentation and were negative. Initial renal ultrasound showed no significant abnormalities.

On hospital day 2, the patient remained alert but complained of abdominal pain and was oliguric. Hemodialysis was continued and hepatic transaminases were noted to be elevated [ALT 354 U/L (normal: 21-72 U/L) and AST 554 U/L (normal: 17-59 U/L)]

What is the significance of the hepatotoxicity?

Several case reports have noted elevated hepatic transaminases, and most have begun N-acetylcysteine therapy. The hepatic injury appears to be less important than the nephrotoxicity, but NAC therapy is relatively benign and most experts would recommend it. Our case was treated with NAC for several days, and his transaminases returned to normal. He never had evidence of hepatic dysfunction, such as coagulopathy or hyperbilirubinemia.

What initial signs on presentation can be used to predict neurologic toxicity?

Most recently, Alfred et al reported an epidemic poisoning where seven inmates at a correctional facility drank varying amounts of DEG. Despite rapid diagnosis and early hemodialysis, they observed delayed neurologic complications. Most developed these complications within the first week post-ingestion. These included cranial and peripheral sensorimotor peripheral neuropathies, encephalopathy, and even seizures. This was the first case series to elucidate the fact that renal injury is a marker for subsequent neurologic sequelae. Their patients with minimal exposures and no renal failure did not develop neurologic complications.

Over the next several days, our patient developed progressive lethargy, dysphonia, facial diparesis, dilated non-reactive pupils, loss of corneal and gag reflexes, and loss of visual and auditory function. By hospital day 6, he developed acute encephalopathy with moderate to severe diffuse slowing on EEG. An EMG/NCV performed at this time showed a generalized sensori-motor peripheral neuropathy with questionable evidence of demyelination.

Are steroids useful for the neuropathy?

Several of the recent case reports with neuropathy treated with steroids have seen improvement in the neuropathy.

There are not enough cases to know whether this therapy affected the outcome, and there are certainly no controlled studies of this therapy.

What was the outcome of this case?

Despite high-dose steroid treatment for the progressive neuropathy, our patient became quadraparetic and was intubated for respiratory failure on hospital day 12. He remained ventilator-dependent and unresponsive until hospital day 47, when he regained pupillary light reflexes. On hospital day 56, repeat EMG/NCV studies showed worsened severe demyelinating sensorimotor peripheral polyneuropathy. Renal ultrasound performed on hospital day 75 showed markedly atrophic kidneys with severe cortical thinning, indicating that he will require life-long hemodialysis (or renal transplantation). His neurologic status continued to slowly improve to the point where he could stand and walk a few steps with assistance, and he was transferred to a chronic rehabilitation center on hospital day 97. At 6 months, his neurologic function continued to improve and he was discharged to home, able to stand and walk with a walker.



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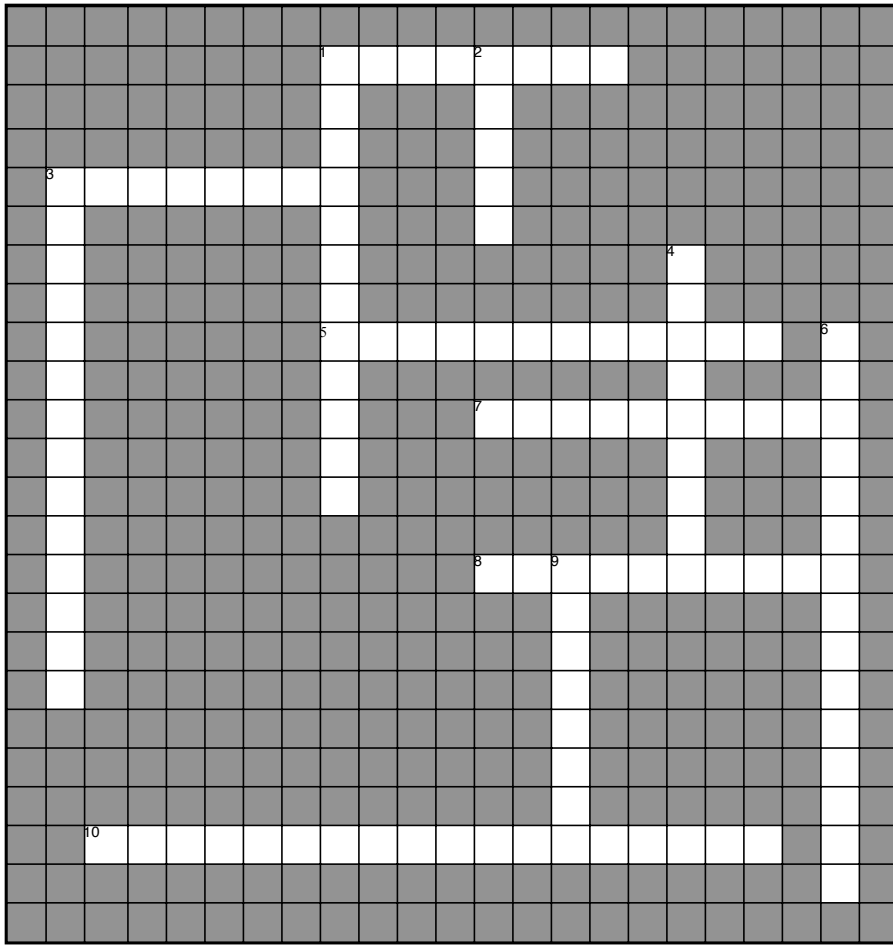
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TOXICOLOGY CROSSWORD FOOD POISONING

Contributed by: Margo M. Spain, RN, CSPI, Upstate New York Poison Control Center, Syracuse, NY



Across

1. Profuse watery diarrhea
3. Spore forming gram (-) rod, N/V, dysphagia, descending paralysis
5. Puffer, fish, na channel blockade, parathesia of lips, tongue, etc.
7. Caused by eating large reef fish, sensory reversal to follow
8. Caused by poultry, eggs, raw milk, pets (turtles, lizards), fever and distention, rose spots, enlarged spleen
10. Shortest onset of temporary vomiting

Down

1. Tuna, mahi mahi, mackerel, peppery taste, histamine effect
2. Hemorrhagic colitis
3. Toxin associated with chinese restaurants and eating reheated fried rice
4. Paralytic shellfish consumption, cranial nerve dysfunction/paralysis
6. Produces ciguatera toxin when eaten by reef fish
9. Food sources include unpasteurized milk, undercooked chicken, symptoms include fever, headache, muscleache

Answers: Across: 1. Shigella; 3. Botulism; 5. Tetrodotoxin; 7. Ciguatera toxin; 8. Salmonella; 10. Staphylococcus Aureus; Down: 1. Scombrototoxin; 2. E. Coli; 3. Bacillus cereus; 4. Saxitoxin; 6. Dinoflagellates; 9. Listeria; Tox Trivia: 1. Acetadote[®]; 2. Wallpaper stripper; 3. Yes; NYPC Tidbits: 1. diethylene glycol; 2. renal failure; 3. False

Diethylene Glycol and Neurologic Toxicity

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SPI CORNER TOPIC: **Oral N-acetylcysteine (N-AC, Mucomist®) and Intravenous (Acetadote®)**

Contributed by: Mary Halsey-Claps, RN, CSPI, Upstate New York Poison Center, Syracuse, NY

As the availability of products containing acetaminophen continues to flood the market, health care practitioners are faced with a need to treat overdoses in health care facilities. N-Acetylcysteine (NAC) is used orally or intravenously (IV) as an antidote for acetaminophen (APAP) toxicity.

In acute overdoses N-Acetylcysteine (NAC), especially if administered within 8 hours, prevents hepatotoxicity. It also has merit when administered within 24 hours or longer after acetaminophen toxicity.

Oral N-acetylcysteine has been successfully administered for years as an antidote, but oral dosing poses some challenges for health care practitioners. Oral N-acetylcysteine is available in 10-20% solutions it must be diluted to 5% to increase palatability. If administered by nasal-gastric tube it must also be diluted. Nausea and vomiting can occur after administration. If a dose is not retained for one hour, it is necessary for repeat dosing. Nausea can be mitigated using antiemetics such as ondansetron or metoclopramide. Dosing includes 140 mg/kg as a loading dose followed by 70 mg/kg every four hours for the duration of therapy.

Historically, patients who are unable to tolerate oral NAC, due to protracted emesis, lack of gastrointestinal tract

integrity or severe hypotension were provided oral NAC in an IV formulation. More recently, a commercially available IV antidote became available called Acetadote®. Acetadote has an advantage in causing less nausea and vomiting as well as having an approved shorter course of therapy for patients presenting before 8 hours after ingestion. The loading dose is 150mg/kg in 200ml of D5W. First maintenance dose of 50mg/kg is diluted in 500ml of D5W. This is followed by a second maintenance dose of 100mg/kg diluted in 1000ml of D5W. Careful monitoring for anaphylaxis is important. In addition, the optimal amount of D5W required for concentrated solutions in children is not established and fluid and electrolyte abnormalities can occur in children due to the large amount of D5W administered without sodium.

As a final review, N-acetylcysteine is recommended in the following scenarios; a 4 hours or more after ingestion serum level above the Rumack-Matthew, a patient with an unknown time of ingestion with a positive acetaminophen level or elevated liver function tests, or a patient with clinical signs of hepatitis. The length of treatment can be variable depending on the time of presentation and degree of hepatic damage.

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