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

The NY State Poison Centers

# Toxicology Letter

January 2003

Vol. VIII No.1

A Quarterly Publication

## TOXICOLOGY ADVICE CENTERS:

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

**Western New York Poison Center (WNY)**
716.878.7871 • www.chob.edu/poison
**Finger Lakes Regional Poison and Drug Info Center (FL)**
585.273.4155 • stronghealth.com/services/poison/index.cfm
**Central New York Poison Center (CNY)**
315.464.7078 • www.cnypoison.org
**New York City Poison Control Center (NYC)**
212.447.8152
**Long Island Poison and Drug Info Center (LI)**
516.663.4574 • www.LIRPDIC.org

## PROGRAM ANNOUNCEMENT S:

**WNY:**
**FL:** Conference, Thursdays • 1:00-2:00pm
**CNY:** Case Conference, Thursdays • 1:30-2:30pm
**NYC:** Consultants Case Conference • 1/2/03, 2/6/03, 3/6/03
An Intensive Review Course in Clinical Toxicology • 3/13-14/03
**LI:** Biological Terrorist Agents • 1/29/03
How to Evaluate and Provide Management to a Posioned Patient • 2/26/03
Cardiac Drug Emergencies • 3/26/03

*Please call administrative telephone numbers for more information.*

## NYPC TIDBITS:

*Matching: Match the antidote with the poisoning*

A. Atropine
B. Sodium nitrite
C. Flumazenil
D. Naloxone
E. Pyridoxine
F. Sodium Bicarbonate

1. Organophosphate poisoning
2. Cyanide toxicity
3. Benzodiazepine overdose
4. Opioid intoxication
5. Seizure on Isoniazid
6. Tricyclic antidepressant overdose

## TOX TRIVIA: PLANTS

1. Cocaine is derived from the leaves of what plants?

2. Marijuana is a common name from the material obtained from this plant.

3. Ephedrine is the active substance in this Chinese plant.

**Case History**

## ACUTE SALICYLATE TOXICITY

**Contributed by:** Kerry Cronin MD, Thomas Caraccio Pharm D, and Michael McGuigan MD, Long Island Regional Poison and Drug Information Cetner

**Case:**

A 16 year old male stole a vehicle and lead police on a high speed chase which ended in a collision. The patient told the police that he ingested 500 aspirin tablets six hours previously. He was evaluated at a local emergency department and no significant traumatic injuries were noted. After discharge into police custody, he developed abdominal pain and a rapid respiratory rate and was brought back to the emergency department. Initial laboratory data revealed an anion gap metabolic acidosis. An arterial blood gas analysis noted a pH of 7.44 with a mixed respiratory alkalosis and metabolic acidosis. His initial salicylate concentration, drawn approximately 6.5 hours post-ingestion, was 49 mg/dL.

The patient was given a single oral dose of activated charcoal and was started on intravenous fluid containing sodium bicarbonate and potassium. The poison information center was contacted and recommended the immediate transfer of the patient to a facility with the capability to perform hemodialysis. Repeat salicylate concentrations were done at 10.5h, 16.5h, and 18.5h post ingestion and were 56 mg/dL, 105 mg/dL, and 133.8 mg/dL, respectively. Approximately 20 hours post-ingestion, the patient arrived at a tertiary care center, had a seizure, developed cardiopulmonary arrest, and died before hemodialysis could be initiated. The antemortem salicylate concentration was 503 mg/dL.

**What are salicylates and how do they work?**

Salicylates are nonsteroidal anti-inflammatory agents commonly used for their analgesic and antipyretic properties. They act on the cyclooxygenase enzymes to impair peripheral and central prostaglandin biosynthesis; they also inhibit platelet aggregation. The usual recommended dose for adults is 325-650mg/dose every 4 hours, and for children is 10-15mg/kg/dose every 4-6 hours with a maximum of 80mg/kg/24h. The toxic dose of salicylic acid is >150mg/kg.[1]

**How common is salicylate overdose?**

In 2001, there were 20,623 salicylate exposures reported to US Poison Centers, of which 3,232 developed moderate and major outcomes and 72 resulted in death.[2]

**What are the toxic effects of salicylic acid, their mechanisms, and the classic phases of acute salicylate intoxication?**

Salicylate has a direct stimulatory effect on the respiratory center in the brainstem inducing hyperventilation.[3] Salicylate indirectly affects respiration secondary to skeletal muscle stimulation, resulting in an increase in oxygen consumption and carbon dioxide production.[4] Together these stimulatory effects produce a respiratory alkalosis. [3,4]

Salicylate toxicity classically gives rise to an increased anion gap metabolic acidosis, which is the result of various mechanisms. In

*Continued on Page 2*

*Continued from page 1*

**Table 1**

| Category of Toxicity | Amount Ingested | Toxic Manifestations |
|---|---|---|
| Mild | 150-200mg/kg | Nausea, Vomiting, Tinnitus, Hyperventilation and Respiratory Alkalosis |
| Moderate | 200-300mg/kg | Hyperpnea, Fever, Acidosis, Lethargy, Dehydration, Mixed respiratory alkalosis and anion gap metabolic acidosis, Electrolyte disturbances |
| Severe | 300-500mg/kg | Altered level of consciousness, Coma, Convulsions, Pulmonary Edema, Hypotension, Renal Failure, Mixed respiratory alkalosis and anion gap metabolic acidosis, Electrolyte disturbances |
| Very Severe | >500mg/kg | Potentially Fatal |

response to the respiratory alkalosis described above, the kidneys increase bicarbonate and potassium excretion.[5] Impaired renal function secondary to salicylate toxicity leads to the accumulation of sulfuric and phosphoric acids.[6] Salicylates alter carbohydrate metabolism, producing hypoglycemia, and interfere with the Krebs cycle's dehydrogenase and aminotransferase enzymes, resulting in the formation of increased lactate, pyruvate, and ketones.[7] In addition, salicylates interfere with cellular metabolism by uncoupling mitochondrial oxidative phosphorylation, resulting in decreased production of ATP and increased acid production and heat generation leading to hyperthermia.[8] Finally, salicylates themselves are weak acids.[7] ***Together these effects of salicylates pr***Salicylates decrease the production of prostaglandins. This may result in gastritis, nausea and vomiting because prostaglandins normally provide gastric mucosal protection.[9] Antiplatelet activity is a well-known effect of acetylated salicylate (aspirin) and rarely hemorrhage may occur with toxicity.[5] Chronic administration of salicylates in large doses causes damage to the liver resulting in prolonged prothrombin time, decreased factor VIII production, and increased capillary fragility, although permanent damage to the liver is rare.[9] Electrolyte disturbances include hypocalcemia, hypomagnesemia, hypokalemia, and hypoglycemia.

The pathophysiologic changes attributable to salicylate toxicity result in various clinical manifestations depending on the amount ingested (Table 1).[5,9,10,11,12]

The most important sign of severe intoxication is an altered level of consciousness. Rare complications of salicylate overdose are GI perforation, inappropriate secretion of antidiuretic hormone, pancreatitis and cerebral edema.

**What is the proper treatment of salicylate overdose?**

Decontamination serves to reduce the absorption of salicylate in overdose situations and numerous decontamination methods are debated in the literature. Acetylsalicylic acid (ASA) absorption is reduced with activated charcoal administration.[13] The recommended dose of activated charcoal is 1-2g/kg, recommended if the patient has ingested a potentially toxic amount of salicylate up to 1 hour previously.[14] There are insufficient data to support or exclude its use after 1 hour of ingestion.[14] Multiple dose activated charcoal (MDAC) is no longer advised in salicylate overdose.[15] Enteric-coated and sustained-release aspirin preparations merit special considerations in regard to GI decontamination.[5] These preparations may be too large for removal by a #40 french gastric lavage tube, may be radioopague depending upon the manufacturer and therefore visualized with abdominal radiographs, and these preparations may form large concretions in the GI tract leading to delayed toxicity.[5] Whole bowel irrigation (WBI) may be considered for potentially toxic ingestions of sustained-release or enteric-coated aspirin tablets[16]. Kirshenbaum et. al. showed that WBI was more effective in reducing the absorption of sustained release aspirin than activated charcoal with sorbitol.[17] Gastric lavage is a consideration, if a life threatening amount was taken, the airway is protected, and the procedure can be undertaken within 60 minutes of ingestion. Although syrup of ipecac is not routinely recommended [19] , some toxicologists may advise it in very large ingestions. Despite the above recommendations for GI decontamination, there is extensive variability in the advice given to health care providers offered by poison control centers.[20]

The treatment of symptomatic patients with salicylate ingestion should be started immediately. The Done nomogram, which was created to identify the level of salicylate intoxication that should prompt intervention, is often misused and misunderstood.[5] It is generally considered to be obsolete [5.] The patient's clinical condition and early course should serve as the guide for clinical therapy[5] After initial stabilization, careful history and physical examination, an assessment of the patient's fluid balance and electrolyte status is necessary. ECG, pulse oximetry, cardiac monitoring, serum electrolyte levels including magnesium and phosphorus, glucose, ABG, renal and hepatic functions, prothrombin time, urinalysis, abdominal radiography, acetaminophen and salicylate levels are recommended. The ABG, electrolytes, glucose level and salicylate level should be repeated in moderate and severe overdose every two hours until the levels are declining and the patient's clinical condition stabilizes.

The goal of salicylate management is to minimize the CNS salicylate concentration and to facilitate salicylate excretion.[5] Intravenous sodium bicarbonate, through alkalinization of the blood and urine, keeps salicylate out of the CSF and enhances urinary salicylate excretion.[21] NaHCO3 should be administered in all but mild salicylate overdoses to produce a pH of 7.4-7.5 and urine pH>7.[22] Adults should receive a bolus 1-2 mEq/kg of sodium bicarbonate followed by an infusion of 100-150mEq NaHCO3 added to 500-100ml of 5% dextrose; children should receive a bolus of 1-2mEq/kg of NaHCO3 followed by an infusion of 1-2 mEq/kg added to 20 mL/kg of 5% dextrose.[22] Target urinary output is >2ml/kg/hr.[22]

*Continued on Page 3*

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Intravenous fluids should contain glucose and potassium. Along with aggressive fluid and electrolyte replacement and alkalinization of blood and urine, symptomatic and supportive care should be instituted. Seizures should be treated with diazepam or lorazepam. Pulmonary edema management consists of fluid restriction, high FiO2, mechanical ventilation and PEEP. Hyperpyrexia is managed with external cooling measures.

Extracorporeal measures are indicated in severe salicylate intoxication. [21] Hemodialysis is considered the best choice because it can rapidly correct acid-base and electrolyte abnormalities while removing salicylate from the blood.[5] Indications for hemodialysis include renal failure, congestive heart failure, persistant CNS disturbances, progressive deterioration of vital signs, severe acid-base or electrolyte imbalance despite appropriate treatment, hepatic compromise with coagulopathy, and salicylate level (acute) >100mg/dL.[21] Higgins et. al. described an interesting case of a man who took two aspirin overdoses in a short space of time, achieving similar blood levels of salicylate and sustaining grand mal seizures on both occasions. On one occasion he was treated with alkalinization and on the other he was treated with hemodialysis; both methods were equally effective in eliminating salicylate over a 24h period, though alkalinization achieved a more rapid initial reduction in blood levels of salicylate.[23]

**What is the difference between acute and chronic salicylate overdose?**

The presentation of chronic salicylate intoxication is more subtle and difficult to diagnose. [24] Chronic salicylism is more common than generally appreciated and is more serious than acute intoxication because it is often under diagnosed. [24] The mortality rate is high with chronic toxicity and the salicylate plasma concentration does not often correlate with the clinical manifestations of toxicity. The young and elderly are often victims of therapeutic errors and are at risk for chronic salicylism. Chronic salicylism is associated with exaggerated CNS findings of lethargy, confusion, drowsiness, slurred speech, hallucinations, tremor, agitation, and delerium.[24] Although there is considerable overlap with some of the presenting signs and symptoms of acute salicylate poisoning, there is a slower onset and a less-severe appearance of these signs with chronic toxicity. [21] The cardinal clinical and laboratory features of chronic salicylate poisoning include abdominal pain, tachypnea, encephalopathy, acid-base disturbances, coagulapathy, and adult respiratory distress syndrome. [25]

**Case discussion:**

Aspirin bezoars, or large concretions, may form after large ingestions of aspirin leading to prolonged absorption. Peak serum salicylate levels may be delayed from 10-60 hours with enteric-coated, sustained-release, or very large ingestions. Although the serum salicylate levels were steadily rising in this patient, appropriate treatment was delayed. Failure of aggressive management in this particular case may have lead to the demise of the patient. Furthermore, despite a history of the ingesting 500 aspirin tablets six hours prior to his presentation, he was discharged without a serum salicylate concentration determination.

***Bibliography***


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**CNYPCC Tidbits answers:**

A. 1
B. 2
C. 3
D. 4
E. 5
F. 6

**Tox Trivia answers:**

1. Erythroxylon coca and Truxillo coca.
2. Cannabis sativa
3. Ma-huang

## SPI CORNER TOPIC: IS GASTROINTESTINAL DECONTAMINATION ALL WASHED UP?

**Submitted by:** The Long Island Regional Poison and Drug Information Center SPI Staff

An important and debated issue in clinical toxicology is whether, when and how to remove ingested poisons from the gastrointestinal tract. Guidelines have been published recently on the use of ipecac syrup, gastric lavage, actiavted charcoal, cathartics, and whole bowel irrigation. The key points regarding these procedures are presented. GI Decontamination (GID) should not be a routine procedure, and should not pre-empt the provision of symptomatic and supportive care. The substance ingested, clinical presentation, and the time of ingestion need to be taken into consideration. GID procedures do not completely evacuate the stomach, and may leave substantial amounts of the ingested substance.

**Syrup of Ipecac** (SOI)is available as a nonprescription drug to produce emesis and remove ingested poisons from the stomach. However, the amount of substance removed by ipecac is highly variable and diminishes with time. SOI should rarely be used in the Emergency Department. Ipecac may delay the administration of activated charcoal or whole bowel irrigation. Ipecac should not be administered to a patient who has a decreased level or impending loss of consciousness or who has ingested a corrosive substance or hydrocarbon with high aspiration potential.

**Gastric Lavage** (GL) involves the passage of an orogastric tube and the sequential administration and aspiration of small volumes of liquid to remove toxic substances in the stomach. There is a difference between GL and gastric aspiration (which involves the use of a smaller tube to suck out liquid from the stomach). The amount of substance removed by GL is highly variable and diminishes with time. There is no evidence that its use improves clinical outcome and it may cause significant morbidity. GL should not be considered unless a patient has ingested a potentially life-threatening amount of a poison, the procedure can be undertaken within 60 minutes of ingestionand the airway is protected with the _____.

**Activated Charcoal** (AC) therapy involves the oral administration or instillation by a tube of an aqueous suspension of AC after the ingestion of a poison. AC physically binds poisons in the gastrointestinal tract, decreasing the extent of absorption of the poison and reducing or preventing systemic toxicity. The greatest benefit from AC is within 1 hr of ingestion. It is contraindicated if airway protective reflexes are lost in a patient who is not intubated; pulmonary aspiration of AC is hazardous.

**Cathartics** such as accharide cathartics (sorbitol) and saline cathartics (magnesium citrate or sulfate, sodium sulfate) attempt to decrease the absorption of substances by reducing GI transit time. Sorbitol improves the palatability of AC by imparting a sweet taste and by masking the grittiness of the charcoal. A cathartic, with or without AC, does not reduce the absorption of drugs or improve the outcome of poisoned patients. The routine use of a cathartic in combination with AC is not recommended.

**Whole Bowel Irrigation** (WBI) cleanses the bowel by the enteral administration of large amounts of an osmotically balanced polyethylene glycol electrolyte solution which physically expels intraluminal contents. There is some evidence that WBI decreases the absorption of ingested drugs, but there is no conclusive evidence that WBI improves the outcome of the poisoned patient. WBI may be considered for potentially toxic ingestions of sustained-release or enteric-coated drugs or substances that are not bound by AC (e.g., iron, lithium). WBI is contraindicated in patients with bowel obstruction, perforation, ileus, and in patients with hemodynamic instability or compromised unprotected airways. Administration of AC during WBI is not recommended.

***References:***

*American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists Position Statements on Gut Decontamination in J Toxicol - Clin Toxicol 1997:35:495-762.*

*American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists Position Statement: Use of Multiple Dose Activated Charcoal in the Treatment of Acute Poisoning in J Toxicol - Clin Toxicol 1999:37:731-751.*

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CNY Poison Center
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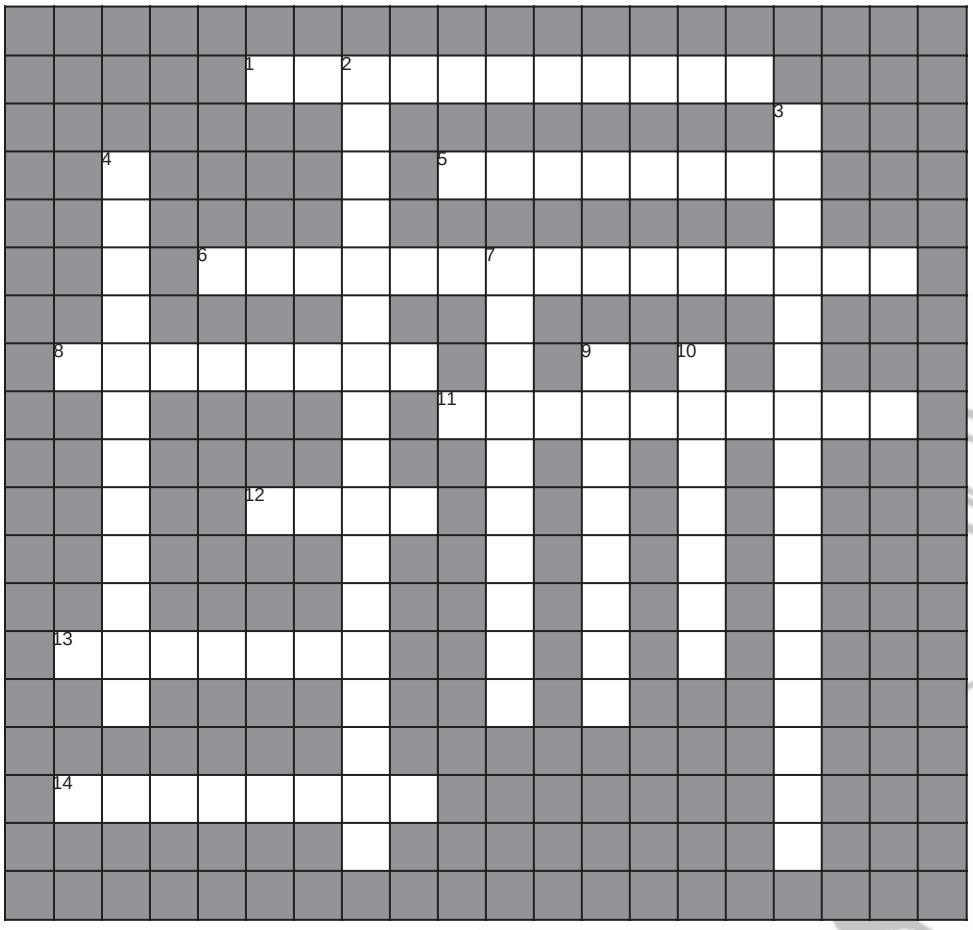
Syracuse, NY 13210

# CROSSWORD PUZZLE : COLD SEASON



1. Antidote for acetaminophen overdose
2. Treat this overdose with deferoxamine
3. Pathognomonic rhythm disturbance is bi-directional ventricular tachycardia
4. Overdose causes agitation, tachycardia, mydriasis, urinary retention, and ileus
5. Treatment of ethylene glycol poisoning
6. Alcohol poisoning causing visual disturbances and fundoscopic abnormalities
7. Toxicity causes coarse tremor, rash, diabetes insipidus, fasciculations and seizures
8. First line agent to treat beta blocker overdose
9. Treatment for a patient with lead poisoning and encephalopathy
10. Calcium gluconate gel is used to treat burns caused by this acid
11. Pulse -ox of 85% with chocolate-brown discoloration
12. Spider bite causing necrosis
13. A date rape drug
14. Mushroom toxin

**Crossword answers:**

1. Nacetylcysteine 2. Iron 3. Digoxin 4. Anticholinergics 5. Fomepizole 6. Methanol 7. Lithium 8. Glucagon 9. Dimercaprol 10. Hydrofluoric 11. Methemoglobinemia 12. Loxosceles 13. Rohypnol 14. Amatoxin

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April 2003

The NY State Poison Centers

# TOXICOLOGY LETTER

A Quarterly Publication • Vol. VIII No. 2

## NYPC Tidbits • •

**Matching:** Match the toxicity with the poisoning.

| | |
|---|---|
| A. Ototoxicity | 1. Methanol |
| B. Nephrotoxicity | 2. Aspirin |
| C. Hepatotoxicity | 3. Penny royal oil |
| D. Ophthalmic toxicity | 4. Propoxyphene |
| E. Cardiotoxicity | 5. Ethylene glycol |

## Tox Trivia • •

1. Orhanophosphates will prolong the action of which neuromuscular blocker?
2. Enhanced elimination of Phenobarbital poisoning can be accomplished using which GI decontamination technique?
3. An unlikely antidote for paraquat poisoning (an herbicide).

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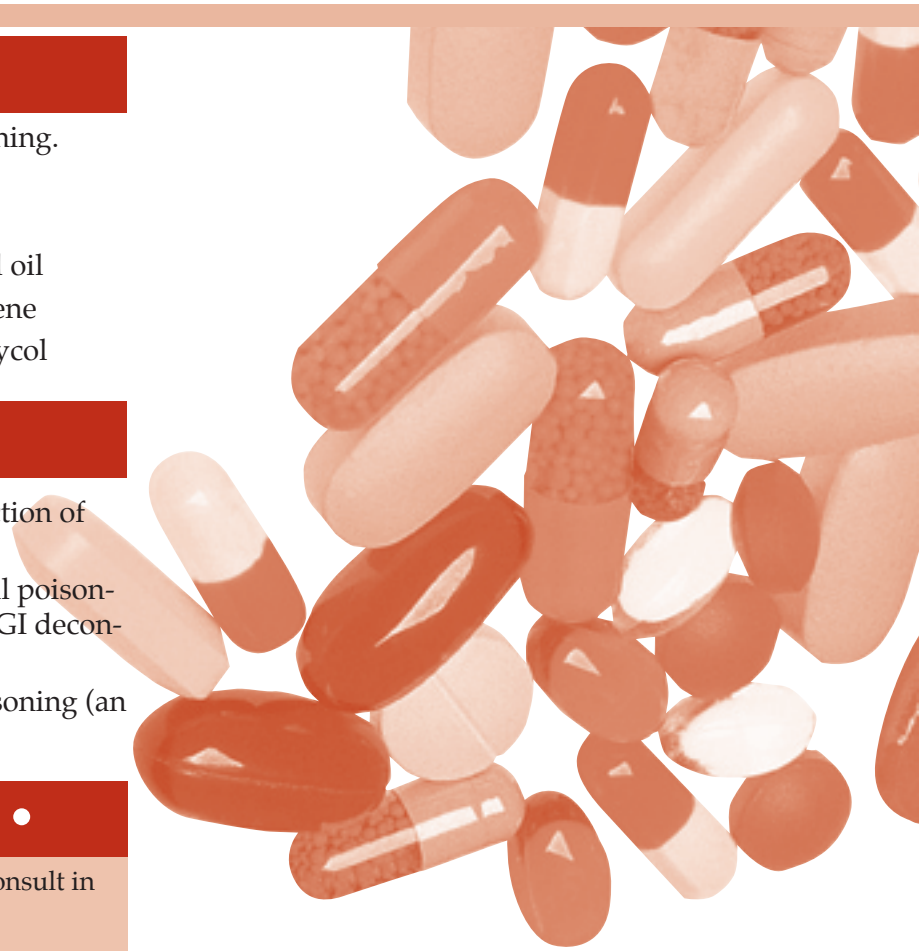
**New York City Poison Control Center (NYC)**
212.447.8152

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

## Answers • •

**NYPC Tidbits answers:** A:2, B:5, C:3, D:1, E:4

**Tox Trivia answers:** 1. succinylcholine
2. activated charcoal
3. fullers earth



## Program Announcements • •

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

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

**Please mark your calendars** for the Seventh Annual Toxicology Teaching Day on October 29, 2003. More information to follow...

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

An Intensive Review Course in Clinical Toxicology

**LI:** See page 5 for information

**Please call administrative telephone numbers for more information.**

# FDA Safety Summaries 1/03 - 3/03

- **Lindane (gamma-hexachlorocyclohexane)** -FDA issued a Public Health Advisory concerning the use of topical formulations of Lindane Lotion and Lindane Shampoo for the treatment of scabies and lice.
- **Procrit (epoetin alfa)** - FDA and Ortho Biotech Products alerted healthcare providers and consumers about the existence of three lots of counterfeit product labeled as Procrit (epoetin alfa): The counterfeit Procrit has been found to be contaminated with bacteria and therefore represents a significant potential hazard to consumers. FDA testing has demonstrated that some counterfeit product contains no active ingredient.
- **Avonex (Interferon beta-1a)** - Updated safety information includes a cautionary note regarding use in patients with depression and other severe psychiatric symptoms. Post-marketing reports of depression, suicidal ideation and/or development of new or worsening of pre-existing psychiatric disorders, including psychosis, and reports of anaphylaxis, pancytopenia, thrombocytopenia, autoimmune disorders of multiple target organs, and hepatic injury manifesting itself as elevated serum enzyme levels and hepatitis were added to the labeling.
- **Ancom Anti-Hypertensive Compound Tablets (Herbal)** – recalled due to containing several prescription drug ingredients, including reserpine, diazepam, promethiazine, and hydrochlorothiazide. [January 17, 2003]
- **Permax (pergolide mesylate)** - revised the WARNINGS section of the prescribing information to inform healthcare professionals of reports of cardiac valvulopathy involving one or more valves in patients receiving Permax therapy. [February 2003]
- **Rapamune (sirolimus)** - notified healthcare professionals of post-marketing reports of bronchial anastomotic dehiscence, including fatal cases, in lung transplant patients treated with Rapamune in combination with tacrolimus and corticosteroids. [February 2003]
- **Serzone (nefazodone HCl)** - notified healthcare professionals of medication errors due to name confusion between Serzone, indicated for the treatment of depression, and Seroquel, indicated for the treatment of schizophrenia. [December 9, 2002]
- **Serevent (salmeterol xinafoate)** - notified healthcare professionals of recent findings from an interim analysis of a large Serevent safety study and a potential association between Serevent and rare, but potentially serious, respiratory adverse events. [January 23, 2003]
- **Prempro/Premphase (conjugated estrogens/ medroxyprogesterone acetate tablets)/ Premarin (conjugated estrogens tablets, USP)** - revised the prescribing information to include a boxed warning, which states that estrogens and estrogens plus progestin therapies should not be used for the prevention of cardiovascular disease. [January 6, 2003]

# Local Anesthetic Toxicity

## Case History:

***Contributed by:*** *Stephanie A. Mallow, Pharm.D., Jeanna Marraffa, Pharm.D., Christine M. Stork, Pharm.D., DABAT, Central New York Poison Center, Syracuse, NY*

**Case:** A 3 year old, otherwise healthy 15kg male was brought to the dentist for a dental extraction and received four 1.5cc intragingival injections of mepivacaine 3% solution prior to the procedure. A total dose of 180mg of mepivacaine was calculated. Shortly after the last injection, the patient experienced a generalized seizure. Intermittent generalized seizures, approximately seven, continued en route to medical care. In the emergency department, he received 1mg of rectal diazepam and 1mg intravenous diazepam, which terminated the seizures.

The patient's past medical history was significant for a febrile seizure. His initial vital signs included: heart rate; 174 beats per minute, blood pressure; 91/60 mmHg, respiratory rate; 35 breaths per minute, temperature; 37.4°C and glucose of 147 mg/dL.

### What is mepivacaine?[1-3]

Mepivacaine (Carbocaine) is a local anesthetic of the amino amide class. Other local anesthetic agents in this class include lidocaine, bupivicaine, and ropivacaine (See Table 1). Mepivacaine is an intermediate-acting agent with a rapid onset of action of 0.5 – 2 minutes in the upper jaw and 1 – 4 minutes in the lower jaw when used for dental procedures. It is approximately 75% protein bound with an elimination half-life of 1.9 to 3.2 hours. It is metabolized primarily in the liver via hepatic hydroxylation and N-demethylation. Mepivacaine is used for paracervical, caudal, epidural and infiltration anesthesia.

### What are the toxic effects and the mechanism of toxicity associated with mepivacaine and related local anesthetics?[1,4-5]

Major toxicity associated with all local anesthetics includes central nervous system (CNS) and cardiotoxic effects. The cause of toxicity is due to either a toxic dose of an agent, a therapeutic dose given too quickly or a therapeutic dose given directly into a blood vessel causing high local concentrations. CNS toxicity includes headache, drowsiness, lightheadedness, shivering, tremors, seizures and coma. These effects are caused by selective blockade of fast sodium channels and inhibition of ϒ–aminobutyric acid (GABA) in cortical cerebral inhibitory pathways causing unopposed excitatory activity. Cardiac toxicity occurs secondary to blockade of the fast sodium channels in the heart, which results in a slowing myocardial automaticiy, cardiac conduction and rate of spontaneous depolarization. This may result in bradycardia, hypotension, myocardial depression, ventricular dysrhythmias and cardiac arrest. In addition, these agents are inducers of oxidative stress, which sometimes results in methemoglobinemia, which is sometimes delayed after initial exposure.

### Does the incidence of toxicity differ between agents?[1-3,5]

While each agent causes both cardiac and CNS toxicity, the physiochemical properties of these agents differ slightly as a result of their chemical structure. Onset of action for a particular agent is based on the drugs pKa. The lower the pKa, the quicker the agent acts. Potency is determined by both the hydrophilic amine, which occupies the sodium channel and the length of the carbon chain providing local anesthetic activity (See Diagram). The duration of action is based on the affinity for protein binding; the more protein bound, the longer the duration of action. Therefore, the different properties of each agent influence the toxicity seen. For example mepivacaine and lidocaine are absorbed and have a faster onset of action than bupivicaine, however bupivicaine has a longer duration of action because it is more extensively protein bound than its counterparts and thus toxicity may be slightly delayed but effects last longer.

### Are dosage adjustments necessary in children and neonates?[6-8]

Weight based dosage adjustments are necessary in children and neonates. Toxicity is associated with serum blood levels, therefore, dosage adjustments on a milligram per kilogram basis should be employed. There is a narrow therapeutic index when using amino-amide local anesthetics in neonates because hepatic function is not mature enough to effectively metabolize these agents resulting in drug accumulation. Neonates also have decreased concentrations of alpha1-acid glycoprotein, which leads to higher concentrations of unbound drug.

### Why is epinephrine added to some of the local anesthetic products?[2]

The addition of epinephrine, or alternative vasoconstrictors, allows for slightly larger doses to be given because it causes vasoconstriction to the localized area, which decreases systemic absorption and increases the duration of local effect. The usual tolerated dose of epinephrine is 0.1mg or 0.2mg otherwise described as 20cc of a 1:200,000 solution or 1:100,000 solution, respectively. In rare circumstances, when

**Continued on page 4**

# Local Anesthetic Toxicity

Continued from page 3

epinephrine is anadvertently administered and enters the venous circulation, severe toxicity can occur. This is manifested by hypertension, tachycardia, and rarely myocardial infarction.

### If a patient is allergic to one of the local anesthetics, are they allergic to all of these agents?[1,5]

There are two different types of local anesthetics, the amino esters and the amino amides (See Table). The major difference between these two classes is how they are metabolized. Amino esters undergo metabolism in the plasma via plasma cholinesterase to the active metabolite para-aminobenzoic acid (PABA). PABA is thought responsible for the allergic reactions seen after use of these agents. The amino amides are metabolized in the liver and do not result in the formation of PABA. Therefore, a patient who has had an allergic reaction to an amino ester should not receive another amino ester compound, but may receive an amino amide without cross-allergenicity. It is important to keep in mind that some of the amino amide agents may contain the preservative methylparaben, which is broken down to PABA and that these agents should also be avoided in a patient with a demonstrated ester allergy. Allergy to an amino amide agent will not result in cross-allergenicity of another amino amide compound, providing the allergenic preservative does not co-exist in each.

### How is local anesthetic toxicity treated?[1,5]

Treatment of CNS toxicity is generally supportive with careful attention to maintaining airway, breathing and circulation. Seizures should be treated using benzodiazepines and if necessary barbiturates followed by general anesthetics. Cardiac toxicity should be treated with advanced cardiopulmonary resuscitation. In the event of hypotension unresponsive to fluids, alpha-adrenergic agonists should be used to maintain adequate blood pressure. Bradycardia should be managed with atropine and/or beta-adrenergic agonists.

### What is Methemoglobinemia, when does it present and how is it treated?[1,9-11]

Methemoglobinemia is a condition in which an oxidizing agent, such as a local anesthetic, causes the heme iron of hemoglobin to be converted from the ferrous (Fe2+) to the ferric (Fe3+) state, thus reducing the ability of hemoglobin to bind and carry oxygen molecules to the body. Acutely, this typically results in 'chocolate brown' colored blood and various degrees of cyanosis, which are unresponsive to 100% supplemental oxygen. Signs and symptoms can range from dyspnea, nausea and tachycardia at lower levels to lethargy, stupor, mental status changes, cardiac arrhythmias and even death at higher levels. The treatment of drug-induced methemoglobinemia is intravenous methylene blue (1-2mg/kg), which is itself an oxidant, but is metabolized by nicotinamide adenine nucleotide phosphate (NADPH) to leukomethylene blue, a reducing agent. It is important to note that deficiency in glucose-6-phosphate dehydrogenase (G6PD) or insufficient NADPH may result in elevated methylene blue levels, resulting in hemolysis.

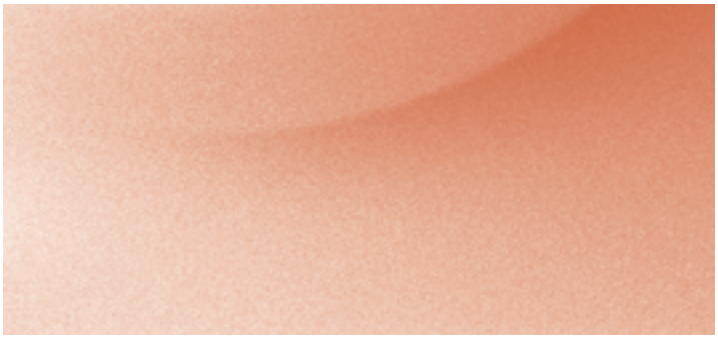
### Patient follow-up.

Following the administration of rectal and intravenous diazepam, seizure activity terminated. Almost immediately following the diazepam, the patient became hemodynamically stable. He was awake, alert and oriented after 2 hours with no further seizure activity. A mepivacaine level was drawn and sent to an outside lab. The level was 2.8mg/L; normal range is 2.0 to 5.0mg/L. Although this level appears to be within the normal range, it was drawn approximately one hour after the injections, and likely a large amount was distributed to other tissues from the original toxic level. This patient received a supratherapeutic dose of mepivacaine, approximately 12mg/kg; maximum dose is 5-6mg/kg in a child. This resulted in initially high blood-brain concentrations leading to the seizures, which resolved with a dose of diazepam and time for the drug to distribute to other body tissues.

### Table 1. Amino Amide vs. Amino Ester[1,2]

| Amino Amide | Amino Ester |
|---|---|
| Lidocaine (Xylocaine) | Procaine (Novocain) |
| Mepivacaine (Carbocaine) | Benzocaine (Cetacaine) |
| Prilocaine (Citanest) | Chloroprocaine (Nesacaine) |
| Bupivacaine (Marcaine) | Tetracaine (Pontocaine) |
| Etidocaine (Duranest) | Cocaine |
| Ropivacaine (Naropin) | |

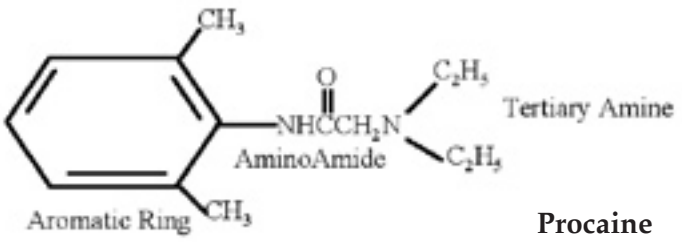
Continued on page 5



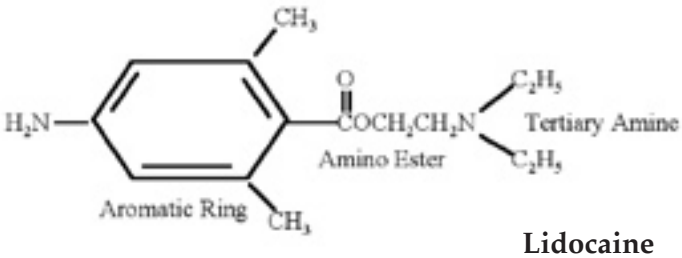
# Local Anesthetic Toxicity

Continued from page 4

**Figure 1. Structural differences of local anesthetics: amide vs. ester [1-3]**




**Procaine**




**Lidocaine**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# Long Island Conferences

Long Island Regional Poison and Drug Information Center will present the following Toxicology Conferences. Continuing Medical Education credits and Nursing CEU are available for all who attend.

Televideo conference can be arranged. Please contact T Caraccio at 516-663-2650 if interested in attending or hooking up online.

**Day/Date/Time**

**Location**

**Topic**

**Presenter**

### Household Toxins

Wed. 4/30/2003:

Time 12:20-1:45PM

Location: WUH New Life Center Conf Rms B & C

Speaker: Gregory Garra, MD

State University NY at Stony Brook ED

### Emergency Drug Testing

Wed. 5/28/2003:

Time 12:20-1:45PM

Location: WUH New Life Center Conf Rms B & C

David Lee, MD

North Shore University Hospital ED

### Antidotes and New Treatments in Poisons

Wed. 6/25/2003:

Time 12:20-1:45PM

Location: WUH WUH Hoag I Conf Ctr

David Juurlink, MD, PhD

Toronto Children's Hospital, Toronto, Canada

# SPI CORNER TOPIC: HIPAA


**Contributed by:** *T. Michele Caliva, RN. CSPI, Operational Director, Central New York Poison Center*

By now, most health care professional are familiar with the HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT OF 1996 or HIPAA. In fact, by April 14th of this year all of us should have completed some type of mandatory HIPPA training. As more hospital staff complete this training, Poison Center staff are meeting resistance when attempting to complete follow up calls on poisoned patients. We hope that the following section will alleviate any concerns that you or your staff may have regarding HIPAA compliance.

Poison Centers in New York State are charged by the New York State Department of Health to follow all hospital-based calls called into the Center and to collect specific information (i.e. type of call, substance, assessment of the patient, nature of the exposure, management and finally medical outcome). Additionally, the Centers for Disease Control recognizes this charge and has issued a grant of authority to the American Association of Poison Control Centers (AAPCC) to conduct public health activities and to function as a public health authority under the HIPAA Privacy Standards under their cooperative arrangement for toxicosurveillance.

Poison centers are also considered a "covered entity" and are recognized as health care providers under the Health Care Provider section (Sec. 160.103). This section defines a health care providers as those who provide medical or health services. Treatment in this section is defined as management of health care by one or more health care providers, also to include a third party consultations. (sec164.501). The Federal Regulation 65:250;82626 12/28/2000 sums this up succinctly:

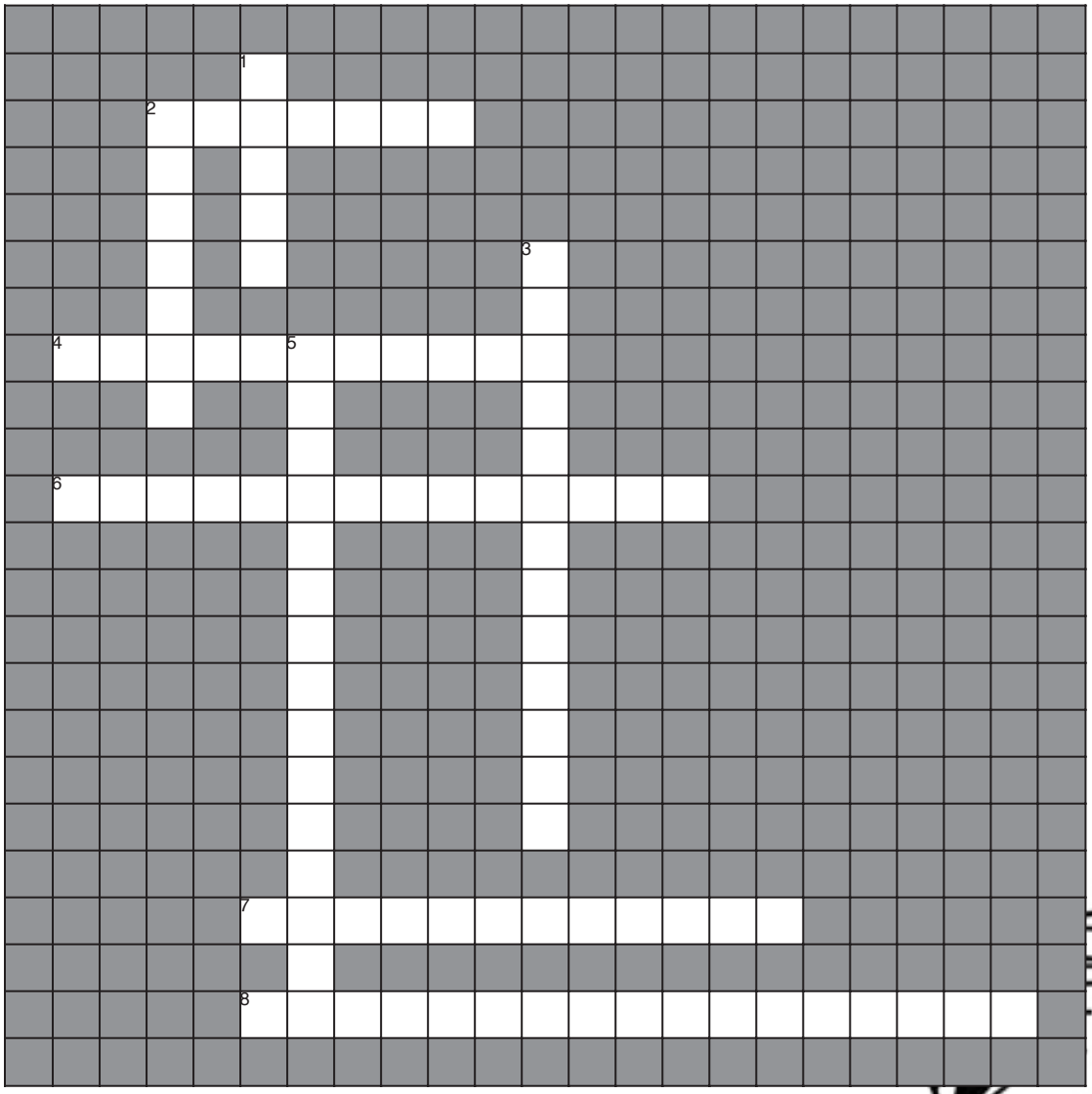
*"We note that poison control centers are health care providers for purposes of this rule. We consider the counseling and follow-up consultations provided by poison control centers with individual providers regarding patient outcomes to be treatment. Therefore poison control centers and other health care providers can share protected health information about the treatment of an individuals without a business associate contract.*

On a practical note, if hospital staff are still reluctant to share information to an anonymous caller, they should disconnect the call and call the poison center back directly at the national 800 number (1.800.222.1222). This will provide assurance that they are indeed talking to a poison center…a covered entity.

# TOXICOLOGY CROSSWORD

## ODORS

*Contributed by Teesh Guenthner, RN, CSPI Central New York Poison Center*



### Down

1. Peanuts
2. Mothballs
3. Rotten eggs
5. Garlic

### Across

2. Bitter almonds
4. Fruity
6. Pears
7. Carrots
8. Wintergreen

**answers:**
**down** 1. Vacor 2. Camphor 3 sulfurdioxide 5. organophosphate
**across** 2. cyanide 4. isopropanol 6. chloral hydrate 7. water hemlock 8. methylsalicylates

State University of New York
Upstate Medical University

**CNY Poison Center**
**750 East Adams Street**
**Syracuse, NY**
**13210**

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

July 2003

The NY State Poison Centers

# TOXICOLOGY LETTER

A Quarterly Publication • Vol. VIII No. 3

## Toxicology Advice Centers • •

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

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

**Finger Lakes Regional Poison & Drug Info Center (FL)**
585.273.4155 • stronghealth.com/services/poison/index.cfm

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

**New York City Poison Control Center (NYC)**
212.447.8152

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

## Program Announcements • •

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

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

**Please mark your calendars** for the Seventh Annual Toxicology Teaching Day on October 29, 2003. More information to follow...

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

**LI:** Environmental: Indoor Air Toxicology • 9/24/03 Michael A. McGuigan, MD - Medical Director. At the LI Reg Poison & Drug Information Ctr, Winthrop University Hospital.

**Please call administrative telephone numbers for more information.**

## Tox Trivia • •

6. Mud is an effective treatment for bee stings.
   a. `True
   b. `False

Continued with answers on page 6

## NYPC Tidbits • •

1. Most snakes in the United States are considered poisonous.
   a. True
   b. False
2. Which of the following is/are true?
   a. Coral snakes have round pupils, fixed fangs, small heads, and no facial pits.
   b. Cottonmouths (Agkistrodon piscivorus) get their name from their white buccal mucosa.
   c. There are ten families of venomous snakes.
   d. All of the above
   e. A and B
3. Four characteristics generally separate poisonous pit vipers (Crotalidae family) from most nonpoisonous snake species. These include all of the following except:
   a. A triangular or arrow-shaped head
   b. Facial pits located between the nostril and eye
   c. Diamondback patterns
   d. Vertical, elliptical pupils
   e. A single row of subcaudal scales
4. Copperheads:
   a. Have copper-colored heads
   b. Possess rattles
   c. Are also called highland moccasins
   d. All of the above
   e. A and C
5. The typical victim of a pit viper is:
   a. A young female
   b. Bitten on the arm
   c. Bitten in January in the United States
   d. All of the above
   e. None of the above

Answers on page 6

# FDA Safety Summaries 4/03 - 6/03

- **Lipitor (atorvastatin)**

  (May 23, 2003) FDA announced that Albers Medical Distributors, Inc voluntary recalled 3 lots of 10 mg 90-count bottles of the cholesterol-lowering drug Lipitor and is warning healthcare providers and others that these three lots of counterfeit Lipitor represent a potentially significant risk to consumers. FDA's investigation into this matter is continuing.

  (June 9, 2003) Albers expanded their original voluntary recall to include all lots of Lipitor that Albers purchased, which were packaged by Med-Pro.

- **Viga Tablets**

  Best Life International warned consumers not to purchase or consume the product known as Viga. This product, which is being marketed as a dietary supplement, contains the unlabeled drug ingredient sildenafil, which may pose possible serious health risks to some users. Viga is sold in bottles of 30 tablets which are distributed by Best Life International Inc. This product is being promoted for increasing desire, confidence and sexual performance. The product is sold without medical prescription. The interaction between nitrates and sildenafil can result in profound and life-threatening lowering of blood pressure. The use of nitrates in any form is an absolute contraindication for sildenafil users. The potential for this product to be taken by unknowing nitrate users is real, since erectile dysfunction is often a concurrent condition in patients with diabetes, hypertension, hyperlipidemia, smokers and patients with ischemic heart disease.

- **Risperdal (risperidone)**

  Janssen Pharmaceutica and FDA revised the WARNINGS section of the prescribing information for Risperdal (risperidone), indicated for the treatment of schizophrenia. Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL has not been shown to be safe or effective in the treatment of patients with dementia-related psychosis.

- **INTERGEL Adhesion Prevention Solution**

  GYNECARE Worldwide (a Johnson & Johnson Company) and FDA Center for Devices and Radiological Health (CDRH) announced the voluntary market withdrawal of "GYNECARE INTERGEL Adhesion Prevention Solution" from the global market and are urging customers to immediately stop using this device. Post-market reports include late-onset post-operative pain and repeat surgeries following the onset of pain, non-infectious foreign body reactions, and tissue adherence. In some patients a residual material was observed during the repeat surgery.

  This product has been distributed in the following countries; Austria, Canada, Egypt, England, France, Germany, Greece, Ireland, Israel, Italy, Japan, Kuwait, Netherlands, Portugal, Republic of Singapore, Saudi Arabia, Scotland, South Africa, Spain, Sweden, Switzerland, United Arab Emirates and the United States.

- **Vinarol Tablets**

  Ultra Health Laboratories, Inc. and Bionate International, Inc. warned consumers not to purchase or consume a product known as Vinarol tablets, promoted for increasing desire, confidence and sexual performance. This product, marketed as a dietary supplement and sold over the counter as well as via the Internet, contains the unlabeled prescription drug ingredient, sildenafil, which may pose possible serious health risks to some users.

  The interaction between nitrates and sildenafil can result in profound and life-threatening lowering of blood pressure. The use of nitrates in any form is an absolute contraindication for sildenafil users. The potential for this product to be taken by unknowing nitrate users is real, since erectile dysfunction is often a concurrent condition in patients with diabetes, hypertension, hyperlipidemia, smokers and patients with ischemic heart disease.

# Poisonous Snakebite and the New Antivenin

## Case History:

***Contributed by:*** *John G. Benitez, MD, MPH, FACMT, FACPM Associate Professor of Emergency Medicine, Environmental Medicine and Pediatrics University of Rochester Managing Director and Assoc. Medical Director Finger Lakes Regional Poison and Drug Information Center*

Spring is here and summer will soon be upon us. This is a case seen in the recent past.

**Case Report:** a 35 y.o. male was bitten on his finger by a Timber rattlesnake he had captured to take a picture. No history of previous bites. Patient presented anxious, but alert and oriented, with a pulse of 107, BP 150/90, and swelling limited to his finger. Within one hour swelling had extended past wrist to distal forearm and patient reported oral paresthesias. CBC and electrolytes normal, and platelet count was 122 K on presentation. However, platelet count dropped to 17 K in 11/2 hours post-admission. Coagulation studies were normal. Ten vials of Wyeth antivenin were administered initially. His vital signs remained stable with his pulse in the 90's. Swelling progressed to the elbow (4 hours after admission). Platelet count dropped to 12 K. Patient developed facial hives which responded to IV diphenhydramine. On completion of the 10 antivenin vials patient felt fine without any of his previous complaints. By 12 hours post-admission, swelling started to recede, vitals remained normal. By 24 hours post-admission platelets were at 101 K (without transfusions) and by the second day were 119 K, vitals remained normal. His INR had increased from 1.2 to a maximum of 1.4, and fibrin split products were detected two days after admission. Fibrinogen levels remained normal. By four days after admission, pt. remained stable, swelling had decreased to the point he could move his fingers and touch each to his thumb, and was discharged. Of note, there was a shortage of all snake antivenins that summer. Between the hospitals and the zoo enough antivenin was obtained, including additional vials, should they be needed. Only the Wyeth product was available. The new Crotalidae Polyvalent Immune Fab was not available in many part of the country including New York. The poison center helped coordinate adequate supplies of the antivenin. Each poison center maintains a database of specific antidotes and antivenins in the region.

### What are the poisonous snakes of New York?

New York State has three poisonous snakes: timber rattler, massasauga, and the copperhead. The timber rattler (listed as "Threatened" by the NYS Department of Environmental Conservation) has the widest range of distribution (see Figure 1 & 2) while the massasauga (listed as "Endangered") has the smallest range (see Figure 3). These snakes belong to the Crotalidae family. Distinguishing features include a triangular or arrow shaped head, facial pits (between eyes and nostrils), and vertical, elliptical pupils.


*Figure 1. Crotalus horridus (Timber rattler).*


*Figure 2*

**Continued on page 4**

# Poisonous Snakebite and the New Antivenin

Continued from page 3


*Figure 3*

Copperhead geographic distribution is somewhat in between the other two and has a recent distribution as depicted in Figure 4.


*Figure 4*

Of course other snakes could have been imported from other parts of the US or the world. These snakes will not be discussed in this brief article, although treatment of all US crotalidae would be as described here.

## What is in the venom of these snakes?

These snakes contain a mixture of enzymes that make up the venom. Typically, they contain hyaluronidase (which helps hydrolyze connective tissue), proteases (break down proteins and peptides), and phopholipases (hydrolyze lipids) among others. See Table. Luckily, approximately 20% of bites are considered dry bites; no venom is injected in the course of the bite.

| Enzymes found in Crotalidae |
|---|
| Hyaluronidase |
| Protease |
| Phopholipase |
| Transaminase |
| Phosphonoesterase |
| Ribonuclease |
| Deoxyribonuclease |
| DNAase |
| ATPase |
| Phosphatase |
| Endonuclease |

*Table*

## What are the signs and symptoms?

Severity varies with species, amount injected, age and health of victim, season, and other individual variation. Envenomation presents typically with at least one fang mark (may be two to four), with immediate burning, and localized edema. Swelling progresses and can be quite marked, including areas distant from the bite. Venom can affect almost every organ in the body. Dermatologic changes include edema, ecchymosis, vesiculation, and necrosis. Petechia and purpura may appear in some cases. Neurologic changes include facial fasciculations. Hematologic effects include hypofibrinogenemia and thrombocytopenia (timber rattlesnake bites can produce profound thrombocytopenia). Hypotension occurs from a decrease in systemic vascular resistance and third spacing of fluids. Non-cardiogenic edema may occur. Other systemic symptoms include perioral paresthesias, facial fasciculations, weakness, diaphoresis, lightheadedness and nausea.

## First aid

First, causing no more harm is paramount. Removal of possible constricting items such as rings will prevent vascular compromise as edema progresses. Rest and reassurance should be provided. Ice may worsen local necrosis and is to be avoided. Although a constricting band (not a tourniquet) can be used, frequent reassessment should be done to make sure that if edema has progressed then the band should be loosened. Incision and drainage is fraught with dangers including infection, trauma to underlying tissues and should be avoided. Routine wound care should be done. Consultation with a poison center or toxicologist is recommended.

Continued on page 5

# Poisonous Snakebite and the New Antivenin

Continued from page 4

## Antivenin

Specific treatment of a moderate to severely envenomated person was typically done with a horse serum derived polyvalent antivenin. This product is reportedly longer going to be available in the US in the near future. The new product (CroFab) is ovine derived and only includes the Fab portion of the immunoglobulin which decreases adverse effects. See Figure 5. Availability in NYS has been spotty, but the company reports increased production and availability this year. Contact your poison center for help in locating antivenin in your region.

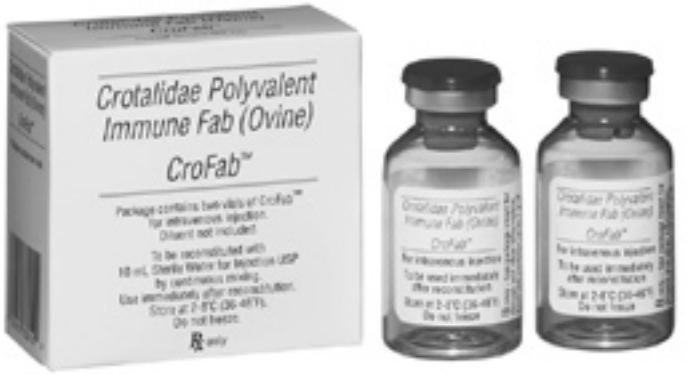



*Figure 5*

Control of all symptoms is now the goal of Fab treatment, followed by maintenance doses of Crotalidae Fab to reduce the incidence of recurrence phenomena. Recurrence is the return of any venom effect after the abnormality had initially been resolved. Two vials every six hours for a total of three doses is the recommended maintenance schedule. Fifty percent of patients not given the scheduled maintenance therapy developed recurrence. Urticaria, wheezing and cough developed acutely in 19% of patients. Symptomatic care was all that was required. Serum sickness developed in 23% of patients. The worst symptoms included hives and urticaria. All were treated successfully with antihistamines and prednisone. In this initial study, it was later found that the Fab lot had excess Fc fragments. A subsequent batch (without the Fc) was tested in 16 patients and only one developed serum sickness. Initial control is obtained by administering 4-6 vials of Crotalidae Fab initially. If initial control is obtained administer 2 vial doses at 6, 12 and 18 hours. If control is not achieved then administer an additional 4-6 vials of antivenin. When control is achieved then additional doses are given as noted. If no control is achieved one should reconsider the diagnosis and consider giving the alternate product. See Figure 6.

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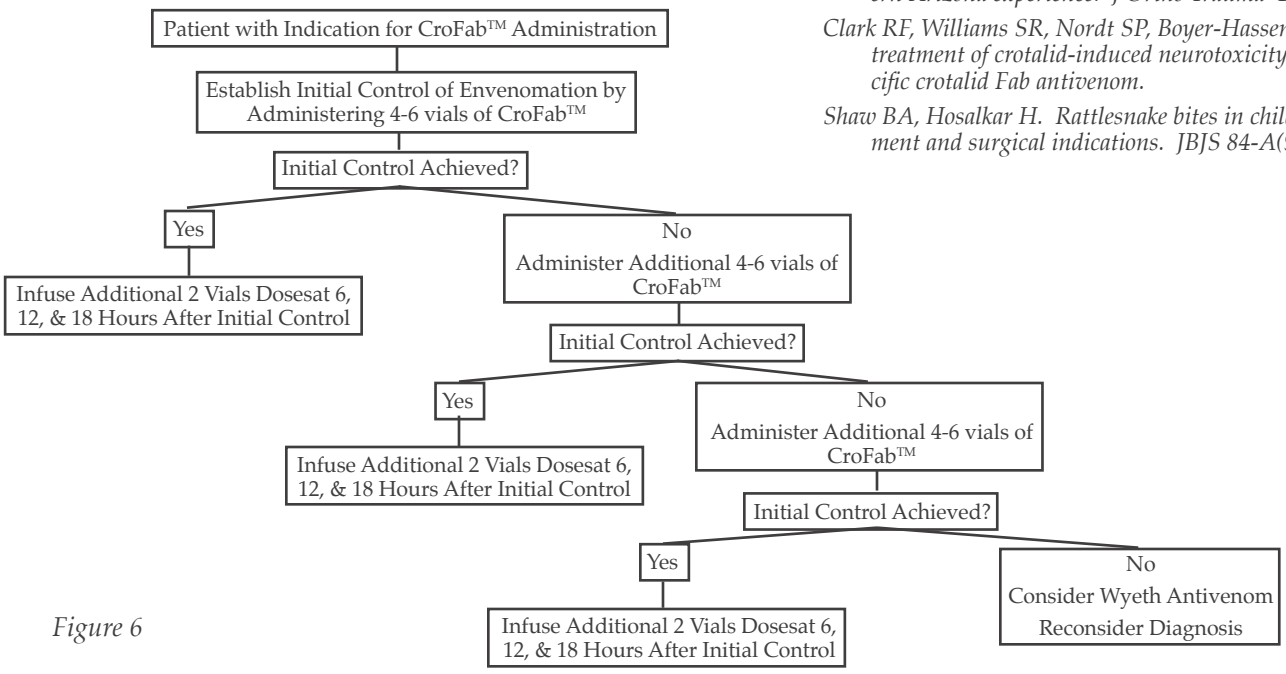



*Figure 6*

# SPI CORNER TOPIC:
# BEES ARE BACK!

**Contributed by:** *Norma Barton, CSPI, Finger Lakes Regional Poison & Drug Information Center*

## Bzzz...

That sound is a familiar one once spring comes and the flowers start blooming. Bees of all sort: hornets, wasps, and honey bees are flying around. Generally, the bees will mind their own business, but occasionally, a human will get in the way. What usually results from a sting is localized pain and swelling. Immediate first aid includes washing the site with soap and water. A cool compress will soothe the discomfort and help relieve swelling. Most times, that therapy is all that is needed. With some stings, the site may be erythematous for awhile and swelling may sometimes linger. Prescribing topical application of hydrocortisone and continued application of cool compress usually suffices. For a very small number of patients, cellulitis may develop. At this point, medical treatment by the primary physician or a visit to the Emergency Department is appropriate. Otherwise, stings can be treated at home. There are exceptions: one is the patient who has an allergy to bee stings and develops anaphylactic reactions. These reactions may include rapid onset of urticaria, angioedema, respiratory distress due to laryngeal edema and/or bronchospasm. Nasal congestion and wheezing, orotracheal edema with difficulty swallowing and breathing, severe hypotension, and cardiovascular collapse may occur. Immediate medical attention is necessary for this patient. Another exception is the patient who is stung numerous times. That patient may require medical attention. If the patient remains at home, they should be watched carefully after the appropriate first-aid treatments previously mentioned are performed.

Those killer bees that seem to be a frequent subject in the news are aggressive and a human may be stung numerous times. The venom is no different than other bees, just that a person is likely to be stung numerous times, increasing chances of developing a severe reaction.

## Some treatment myths

**Mud:** may be soothing, but has no beneficial effects.

**Paste made with Sodium Bicarbonate (baking soda):** no beneficial effects.

Application of some therapies, such as alcohol, may actually be quite irritating.

Any stinger left by the bee should be removed by scraping a dull object, such as a butter knife, along the surface of the skin. Flip the stinger out, being careful not to squeeze the stinger or venom sac.

Other insects and spiders bite and may cause the same type of local non-allergic reaction. Treatment recommendations remain the same as with bees. In these cases, an allergic, systemic reaction is not expected to occur. One symptom that may occur after a spider bite that is not seen with other bites or stings is necrosis. Symptoms that develop after a spider bite may linger for a week or more, also, a patient may be worried that the offending spider is a dreaded Brown Recluse or Black Widow. Neither of these spiders is seen in the Northeast; but any spider can envenomate and cause local effects.

***References:*** *Poisindex*

## Tox Trivia

Continued from page 1

7. Anaphylactic reactions to bee stings include the following:
   a. Angioedema
   b. Respiratory distress
   c. Wheezing
   d. Difficulty swallowing
   e. All of the above
8. Methods of avoiding possible bites and stings include:
   a. Avoiding areas of stagnant water
   b. Wearing long sleeved shirts and pants
   c. Wearing sandals
   d. Playing with snakes
   e. A & B

## Trivia & Tidbits Answers • •

1: B; 2: E; 3: C; 4: E; 5:E; 6:A, 7: E, 8: E

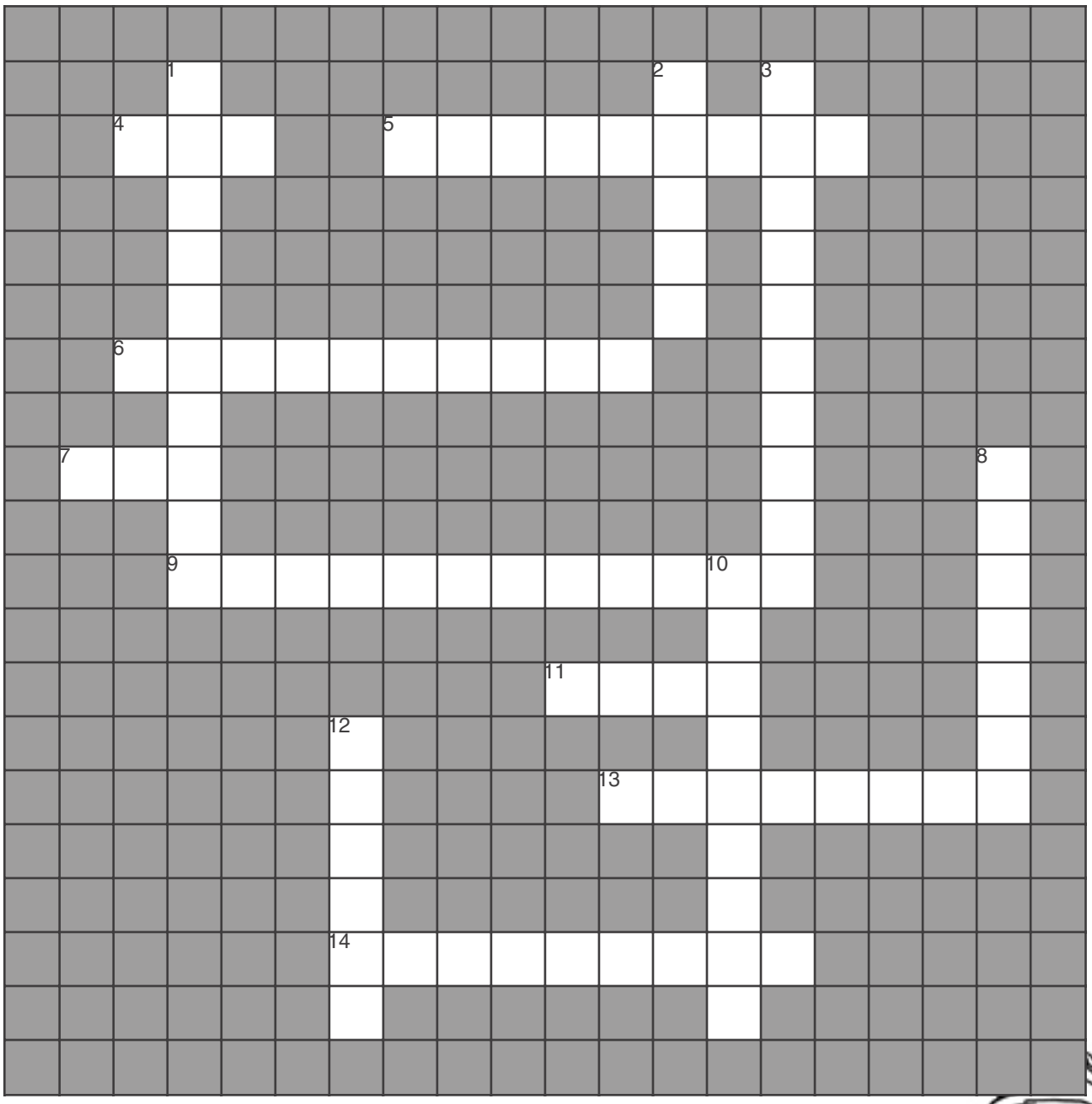
**Crossword answers:**

**down** *1. Crotalidae 2. Gauze 3. Ecchymosis 8. Enzymes 10. Urticaria 12. CroFab™*

**across** *4. Dry 5. Avoidance 6. Black Widow 7. Mud 9. Erythematous 11. Deet 13. Necrosis 14. Antivenin*

# TOXICOLOGY CROSSWORD

# SNAKEBITES



## Down

1. Family "name" of poisonous snakes
2. Mosquito netting made of this
3. Skin discoloration consisting of large hemorrhagic areas
8. A mixture of these make up snake venom
10. Allergic reaction of large wheals
12. Maker of snake bite antivenin

## Across

4. Snake bite in which no venom is injected
5. Method for preventing bites and stings
6. Poisonous spider
7. Bee sting treatment myth
9. Diffuse redness
11. Insect repellant
13. Death of tissue
14. Treatment for snakebite

*answers on page 6*

State University of New York
Upstate Medical University

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**Syracuse, NY**
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New York State Poison Centers
1-800-222-1222

October 2003

The NY State Poison Centers

# TOXICOLOGY LETTER

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## Toxicology Advice Centers • •

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

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

**Finger Lakes Regional Poison & Drug Info Center (FL)**
585.273.4155 • stronghealth.com/services/poison/index.cfm

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

**New York City Poison Control Center (NYC)**
212.447.8152

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

## Program Announcements • •

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

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

**Please mark your calendars** for the Seventh Annual Toxicology Teaching Day on October 29, 2003. More information to follow...

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

**LI:** Environmental: Indoor Air Toxicology • 9/24/03 Michael A. McGuigan, MD - Medical Director. At the LI Reg Poison & Drug Information Ctr, Winthrop University Hospital.

**Please call administrative telephone numbers for more information.**

## Tox Trivia • •

1. Where was the first Poison Control Center in the United States founded?
2. What is believed to be responsible for the Salem witch crisis in 1692?
3. What is the active ingredient in glow sticks?

Answers on page 6

## NYPC Tidbits • •

1. Name 2 toxicologic treatment uses for cellophane (or duct) tape?
2. Name 3 non-waterborne "pets" that may cause toxicity due to their secretions ?
3. What plant contains colchicine?
4. What is the ingredient used in nontoxic antifreeze?

Answers on page 6

# FDA Safety Summaries 7/03 - 9/03

- **Orlaam (levomethadyl acetate hydrochloride)**

  Roxane Laboratories, Inc. is discontinuing the sale and distribution of ORLAAM, a synthetic opioid agonist solution indicated for the management of opiate dependence, reserved as second-line therapy for the treatment of opiate-addicted patients who fail to show acceptable response to other adequate treatments for opiate addiction. ORLAAM was removed from the European market in March 2001 following reports of severe cardiac-related adverse events, including QT interval prolongation, Torsades de Pointes and cardiac arrest. *Sept 2, 2003*

- **Reyataz (atazanavir sulfate)**

  BMS and FDA notified clinicians caring for HIV-infected patients of important new safety data concerning the coadministration of Reyataz (atazanavir sulfate) and Viread (tenofovir disoproxil fumarate.) Clinicians should use caution when administering unboosted Reyataz with tenofovir DF. Unboosted Reyataz may be less effective due to decreased atazanavir concentrations in patients taking Reyataz and tenofovir DF. As a result the coadministration of unboosted Reyataz with tenofovir DF may lead to loss or lack of virologic response and possible resistance to Reyataz. *August 8, 2003*

- **Zenapax (daclizumab)**

  FDA and Roche revised the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and CLINICAL STUDIES sections of the prescribing information to include important new safety information describing the increased mortality seen in a cardiac transplant study and other updated information regarding hypersensitivity reactions. *August 2003*

- **Serevent Inhalation Aerosol (salmeterol xinafoate)**

- **Serevent Diskus (salmeterol xinafoate inhalation powder)**

- **Advair Diskus (fluticasone propionate and salmeterol inhalation powder)**

  The FDA announced the addition of new safety information and warnings to the labeling for drug products that contain salmeterol, a long-acting bronchodilator used to treat asthma and chronic obstructive pulmonary disease (COPD). The new labeling includes a boxed warning about a small, but significant, increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in a recently completed large U.S. safety study. *August 2003*

- **Pyrazinamide plus Rifampin for Treatment of Latent Tuberculosis Infection (LTBI)**

  The Centers for Disease Control and Prevention (CDC) notified healthcare professionals of revised recommendations against the use of rifampin plus pyrazinamide for treatment of latent tuberculosis infection, due to high rates of hospitalization and death from liver injury associated with the combined use of these drugs. *August 8, 2003*
  *[August 8, 2003 - MMWR Article - CDC]*

- **Ziagen (abacavir)**

  GlaxoSmithKline (GSK) notified healthcare professionals of a high rate of -early virologic non-response observed in a GSK-sponsored clinical study of therapy-naive adults with HIV infection receiving once-daily three-drug combination therapy with lamivudine (Epivir, GSK), abacavir (Ziagen, GSK) and tenofovir (Viread, TDF, Gilead Sciences). Based on these results: Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naive or pretreated patients. *July, 2003*

- **Nortrel 7/7/7 - 28 Day Oral Contraceptive (norethindrone and ethinyl estradiol tablets, USP)**

  Barr Laboratories announced a voluntary recall of 3 lots of its Nortrel 7/7/7 – 28 day (norethindrone and ethinyl estradiol tablets, USP) oral contraceptive product. The recall involves Lot Numbers 290122001, 290122002 and 290122003 and is being implemented because two individuals notified the company that the color-coded tablets in their product blister cards were in an improper sequence. *July 9, 2003*

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

  Ortho-McNeil and FDA revised the WARNINGS and PRECAUTIONS sections of the prescribing information to provide updated information about oligohidrosis (decreased sweating) and hyperthermia, which have been reported in topiramate-treated patients. *July 9, 2003*

**Continued on page 5**

# Toxic Myocardial Sensitization

## Case History:

***Contributed by:*** *Howard Greller, MD, Fellow in Medical Toxicology, New York City Poison Control Center*
*Lewis Nelson, MD, FACEP, FACMT, Toxicology Fellowship Director, New York City Poison Control Center, Assistant Professor, Department of Emergency Medicine, New York University School of Medicine*

### Case Report:

A 50 year-old man was brought to the emergency department after being found with an empty bottle (30 cc) of chloral hydrate. He became progressively obtunded following arrival. Vital signs were: BP 128/67 mmHg, pulse 102/min, respiratory rate 25/min, pulse oximeter 97% on 40% $O_2$, and afebrile. The ECG showed a NSR at 67/min, with a QRS of 0.084 sec and a QTc of 0.640 sec. Two hours after arrival, he experienced polymorphic ventricular tachycardia (PVT) associated with hypotension. After successful defibrillation (200 J / 300 J) to sinus tachycardia the patient had a blood pressure of 92/41 mmHg; a lidocaine infusion was initiated. Less than one hour later, during suctioning, PVT recurred and spontaneously converted. During a second suctioning, the patient again developed PVT.

### What is toxic myocardial sensitization?

Myocardial sensitization occurs when the heart is rendered irritable and exhibits an exaggerated response to stimulation. In general, sensitization is due to alteration in the normally highly ordered process of depolarization and repolarization. This predisposes the heart to development and propagation of abnormal impulses, potentially leading to malignant dysrhythmias.

Chloral hydrate is a halogenated hydrocarbon, the class of compounds most often associated with myocardial sensitization. Chloral hydrate and the inhalational anesthetics (e.g. halothane) are the only halogenated hydrocarbons used in clinical practice, and each of these agents is capable of increasing myocardial irritability. Workplace exposure to this class of chemicals is common; examples include perchloroethylene (dry cleaning fluid), Freon, and many organic solvents. Hydrocarbons are also associated with inhalational abuse, usually from huffing (soaking a rag with solvent and breathing through it) or bagging (filling a paper bag with hydrocarbon vapors) with easily available chemicals such as butane, glues and paints.

### What is the mechanism for toxic myocardial sensitization?

The process that predisposes a cell to sensitization is an alteration in repolarization, through blockade of the potassium channel ($I_{Kr}$, the delayed rectifier current). Before describing the events and agents that lead to myocardial sensitization, one must review the events involved in the propagation of the impulse. Although they have very different functions within the heart, both conduction and contractile cells are mechanistically similar. The following describes the propagation of impulse in a generic myocardial cell.

The cell cycle begins with alteration in the state of the fast sodium channel, which leads to a rapid influx of sodium. This is phase 0 of the myocardial action potential, and is represented on the surface ECG by the QRS complex. With the rapid influx of sodium, the myocardial cell potential changes from its resting potential near – 80 mV to near + 30 mV. At this point, a proportion of the fast sodium channels become inactive, preventing the influx of sodium, significantly reducing the rapid inward current. This is phase 1 of the cycle.

Depolarization leads to opening of the voltage-gated L-type $Ca^{2+}$ channel, leading to an influx of calcium. This is phase 2 of the cycle, and is represented by a plateau of membrane potential. The plateau is the electrical balance between the efflux of potassium and the influx of calcium. The small change in the micromolar concentration of intracellular calcium triggers calcium-dependent calcium release from the sarcoplasmic reticulum (SR). This is mediated through the ryanodine receptor. The large efflux of calcium from the SR leads to a cascade of secondary messengers, as well as the disinhibition of troponin on actin/myosin, leading to contraction of the cell.

With termination of the influx of calcium, the cell repolarizes through the combination of restoration of calcium balance and the rapid extrusion of potassium. This is phase 3 of the cycle, represented by the T wave on the ECG.

Calcium balance is restored through a combination of mechanisms. First, influx of calcium is reduced with the inactivation of the L-type calcium channel. Next, the SR takes up the majority of the pool of intracellular calcium. Finally, the $Na^+/Ca^{2+}$ exchanger

Continued on page 4

# Toxic Myocardial Sensitization

Continued from page 3

exchanges extracellular sodium for intracellular calcium in a 3:1 molar ratio (3:2 charge ratio). Intracellular sodium is exchanged for extracellular potassium in a 3:2 molar ratio by the ATP dependent $Na^+/K^+$ pump. Extrusion of sodium, redistribution of calcium, and the efflux of potassium lead to restoration of the resting membrane potential. The period between repolarization and depolarization is phase 4 of the cycle, represented by the isoelectric line or TP segment on the ECG.

## Alterations in the cycle that lead to sensitization

There are two major mechanisms involved in the production of sensitization. The first is dispersion of repolarization; the second is hyperexcitability.

The concept of "dispersion of repolarization" is best explained by the fact that the heart is not a homogeneous structure. Each layer of the myocardium in each anatomic region of the heart is dissimilar in both the concentration and composition of the various channels. Thus, since drugs affect the various channels differently, myocardial cells may exhibit different responses. This predisposes to the formation of abnormal conduction pathways; the ideal substrate for reentry.

The cell becomes hyperexcitable by two processes. When the $I_{Kr}$ channel is blocked, it takes longer for the cell to fully repolarize. The gradual repolarization of the cell keeps the membrane potential between that of fully repolarized and depolarized. On the surface electrocardiogram, slowed repolarization is represented by a prolongation of the QT interval. Over time, the deactivated L-type $Ca^{2+}$ channels become able to reactivate again. If the cell is hovering near the potential needed to activate these channels, they can open, allowing an influx of calcium. This influx of calcium, before the cell is fully repolarized, results in an early afterdepolarization (EAD). If the influx of calcium is sufficient, it can lead to a conducted beat or a contraction. The second process by which the cell can be hyperexcitable is a delayed afterdepolarization (DAD). The DAD occurs once the cell has become repolarized. It is thought that the DAD occurs through spontaneous release of calcium from an already overloaded SR. This in turn can cause the same cascade of events that occurs when the intracellular calcium concentration rises from normal cellular depolarization.

When the cell is hyperexcitable through one of the two above processes, and the dispersion of repolarization has been altered by the agent in question, any abnormal impulse can be propagated in a malignant manner. Thus, the myocardium is primed and triggered for malignant dysrhythmias by the agents involved.

## Chlorinated hydrocarbons

As noted above, chloral hydrate is a chlorinated hydrocarbon. Chlorinated hydrocarbons block the $I_{Kr}$ channel, prolonging repolarization, and leading to EAD. A sudden stimulus or catecholamine surge leads to stimulation of the myocardial cell through the $\alpha$-adrenergic receptor. This leads to a cascade of events mediated through increased intracellular cyclic AMP, ultimately leading to phosphorylation of the L-type calcium channel. This phosphorylation leads to increased calcium influx with each beat. The combination of greater intracellular calcium, EAD, and dispersion of repolarization may lead to malignant dysrhythmias.

## Treatment of the dysrhythmias of sensitization

The treatment of these dysrhythmias follows standard emergency management. The interesting, and often counterintuitive approach to treating these dysrhythmias involves the use of $\alpha$-adrenergic antagonists. As is used to quell the tachydysrhythmias of theophylline overdose (associated with delayed afterdepolarizations due to increased intracellular $Ca^{2+}$), $\alpha$-adrenergic blockade prevents the additional stimulus of endogenous catecholamines from triggering an dysrhythmic event. These events gained prominence with the rash of "sudden sniffing deaths" in the 1950's and 60's, which involved preteens and teenagers who were abusing inhalants. When confronted with an adrenergic stimulus, such as being confronted by law enforcement or a parent, the catecholamine surge triggered a malignant dysrhythmia in a heart already sensitized by the hydrocarbon.

Amiodarone, an additional treatment option, may have theoretical benefit. Amiodarone not only works as a $\alpha$-adrenergic blocking agent, but also blocks potassium, calcium and sodium channels. These actions may help to lessen the sensitization of the myocardial cell.

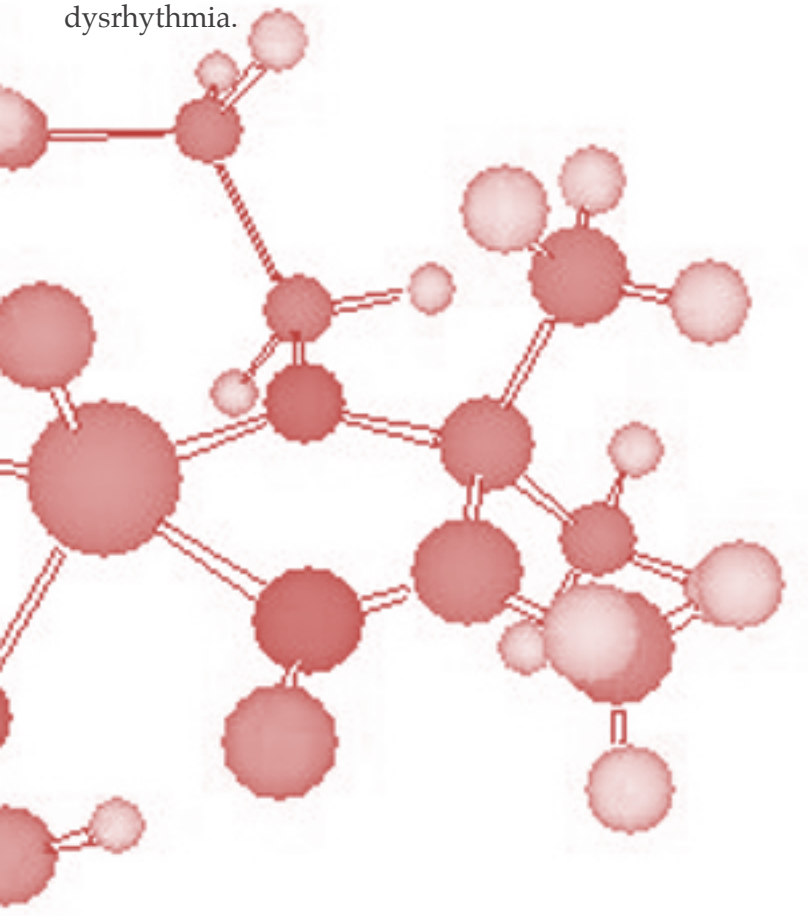
Continued on page 5

# Toxic Myocardial Sensitization

Continued from page 4

## Conclusion

Many agents can cause sensitization of the myocardium. The sensitization occurs through mechanisms that raise intracellular calcium and prolong the repolarization of the cell. In the recent past, a number of pharmaceutical agents have been pulled from the marketplace because of their ability to block $I_{Kr}$, prolong the QT interval, alter dispersion of repolarization, and predispose patients to the development of malignant dysrhythmias such as torsades des pointes. In the setting of a pharmacologic sensitization, any stimulus that causes a catecholamines surge can trigger a malignant dysrhythmia. Along with standard ACLS therapy, ∝-adrenergic antagonists can be used to terminate this excess stimulation, and terminate the dysrhythmia.



## Case Conclusion

The patients second bout of PVT terminated only after a bolus of 150 mg of intravenous amiodarone. The patient was placed on an amiodarone infusion and despite the persistent prolongation of his QTc interval he had no further recurrence of ventricular dysrhythmias, even with recurrent suctioning. After 24 hours, the infusion was discontinued and a subsequent ECG revealed a normal QTc. The patient was placed on oral propranolol and discharged to a psychiatric facility.

## Selected References:


1. *Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001, 345: 1473-82.*
2. *Yang T, Snyders D, Roden D. Drug block of Ikr, model systems and relevance to human arrhythmias. J Cardiovasc Pharmacol 2001, 38: 737-44.*
3. *Nelson LS. Toxicologic myocardial sensitization. J Toxicol Clin Toxicol 2002, 40(7): 867-79.*


# FDA Safety Summaries 7/03 - 9/03

Continued from page 4

- **Health Nutrition (RMA Labs) Viga or Viga for Women Tablets**

  Health Nutrition (RMA Labs) warned consumers not to purchase or consume the products known as Viga or Viga for Women Tablets. These products, which are being marketed as dietary supplements, contain the unlabeled drug ingredient sildenafil, which may pose possible serious health risks to some users. *June 24, 2003*

# Trivia Answers • •

1. Chicago in 1953
2. grain contaminated with ergot alkaloids
3. dibutyl phthalate

**Crossword answers:**

**down** *1. Phenylalkylamine 2. Antagonists 6. Insulindextrose 7. Electrocardiogram*

**across** *3. Nifedipine 4. Calcium 5. Hypotension 8. Ltype 9. Benzothiazepine*

# Tidbits Answers • •

1. to pick up mercury spilled from thermometers or to remove spines from caterpillars that are entrapped in skin
2. salamanders, newts and toads
3. Autumn Crocus
4. propylene glycol

# SPI CORNER TOPIC:
# DEXTROMETHORPHAN ABUSE

***Contributed by:*** *Deborah A. Anguish RN, CSPI. Central New York Poison Center, Syracuse, NY*

Poison Centers are receiving an increasing number of calls concerning Dextromethorphan (DMX) abuse. Many of these calls are from Health Care Providers who are not familiar with this type of abuse. A frequent brand name that is abused by teens is Coricidin HBP. Since the 1960's when DMX was developed and marketed as an over-the-counter antitussive widespread abuse has been reported.

Dextromethorphan is a safe and effective over the counter ingredient in many cough and cold preparations where it is useful as an antitussive. DMX pharmacology includes noncompetitive, non selective antagonism at the NMDA receptor (an excitatory amino acid receptor). As the dextro-isomer of codeine, DMX also binds to specific sites in the central nervous system that are not opioid receptors, but are not yet fully clarified. Many of the effects of DMX intoxication are likely caused by its active metabolite, dextrorphan.

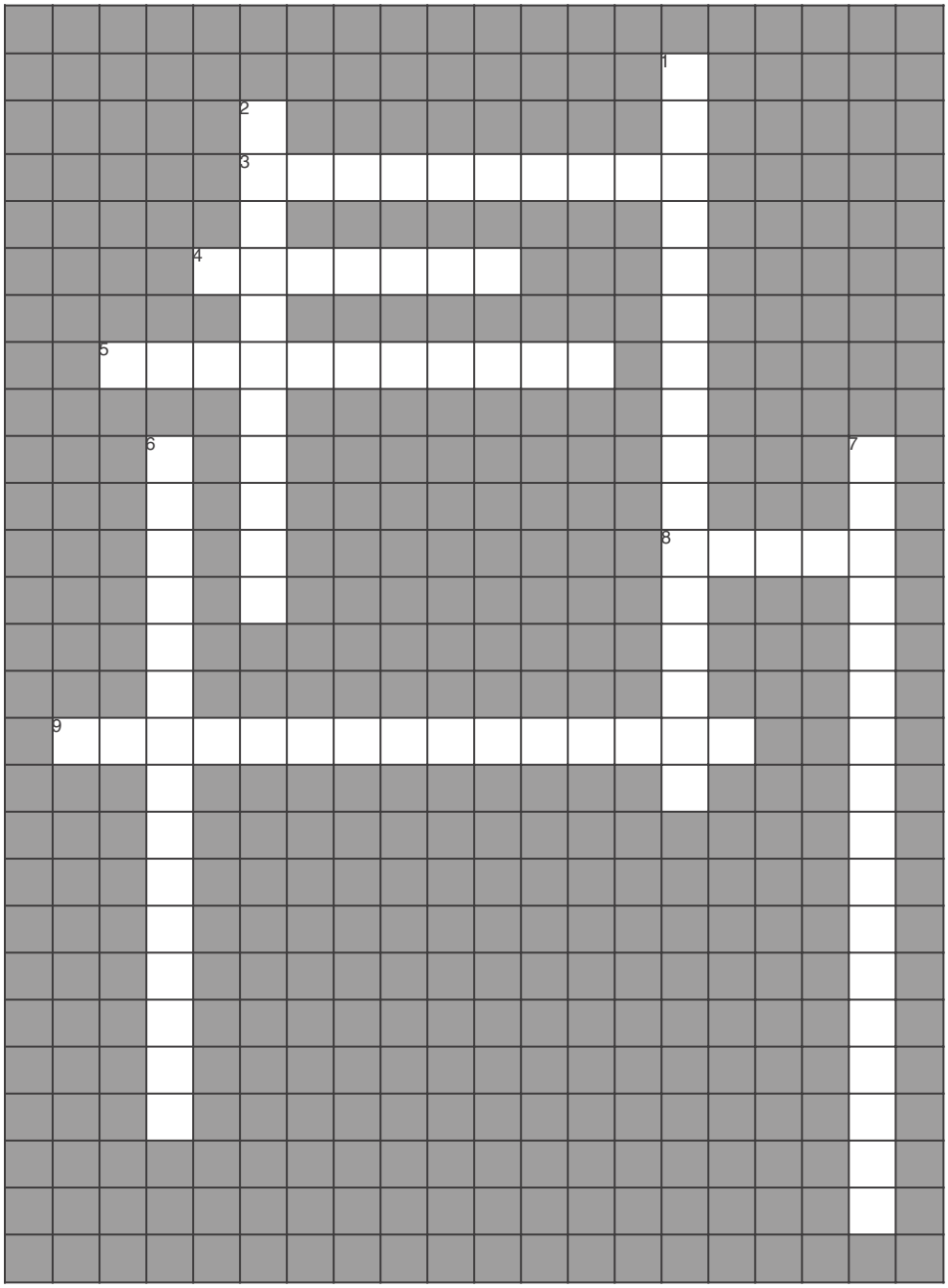
Dextrorphan causes physical symptoms similar to acute phencyclidine (PCP) intoxication. DMX is frequently abused because it provides users with euphoria, sedation, agitation, dissociative sensations, and visual hallucinations when used at high "abuse" doses. DMX can also result in psychological dependence, demonstrated by marked dysphoria and depression when intoxication wears off, but doesn't seem to cause physical dependence. DMX also has serotonigeric properties and thus has the potential to result in Serotonin Syndrome, particularly when used in combination with other agonists at the 5HT-1A receptor site.

Treatment of patients presenting after DMX abuse is largely supportive with careful attention to airway, breathing and circulation. Naloxone has been reportedly used with mixed results. With no reports of adverse effects and a few reports of improvement in symptoms it may be worth trying naloxone for severe intoxications with airway compromise. Benzodiazepines should be used for the treatment of agitation. Many times DMX containing products are ingested in combination with other products commonly found in cough and cold preparations. Assessment and treatment of acetaminophen, aspirin, various antihistamines and decongestants is also prudent.

TOXICOLOGY CROSSWORD

# CALCIUM CHANNEL ANTAGONISTS

*Contributed by the New York City Poison Center*



## Down

1. Verapamil is what class of calcium channel antagonist?
2. What pharmacologic action do these agents have on receptor sites?
6. Name a novel treatment for calcium channel antagonist over dose.
7. What is an important diagnostic tool in calcium channel antagonist overdosed patients?

## Across

3. This calcium channel antagonist is more likely to result in reflex tachycarida than bradycardia after overdose.
4. What is a useful "antidote" for a calcium channel antagonist ingestion?
5. Name one of the major hematologic toxic effects seen with calcium channel antagonists
8. CCB act primarily at which type of calcium channels?
9. Diltiazem is in which class of calcium channel antagonist?

*answers on page 5*

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