



July 2004

The NY State Poison Centers

TOXICOLOGY

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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 • www.chob.edu/poison

Finger Lakes Regional Poison & Drug Info Center (FL)

585.273.4155 • www.FingerLakesPoison.org

Central New York Poison Center (CNY)

315.464.7078 • www.cnypoison.org

New York City Poison Control Center (NYC)

212.447.8152

Long Island Poison & Drug Info Center (LI)

516.663.4574 • www.LIRPDIC.org

Program Announcements • •

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

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

Save the date.

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

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

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

LI: *Critical Care Toxicology*, September 30, 2004 12-2PM by Dr Prashant Joshi.

The conference will be available by both TV or telephone for any health care professional that wants to participate.

Please call administrative telephone numbers for more information.

Tox Trivia • •

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

NYPC Tidbits • •

Match the poison with the pest:

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

Answers on page 6

FDA Safety Summaries April-June, 2004

Paradigm Quick-set Plus Insulin Administration Set

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

Children's Motrin Grape Chewable Tablets

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

Desyrel (trazodone hydrochloride)

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

Oxandrin (oxandrolone, USP)

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

Zelnorm (tegaserod maleate)

The FDA and Novartis notified healthcare professionals of an important drug warning and prescribing information for Zelnorm, a serotonin 5-HT₄ receptor partial agonist indicated for the short-term treatment of women with irritable bowel syndrome (IBS) whose primary bowel symptom is constipation. This new information relates to a Warning for serious consequences of diarrhea and a Precaution for rare reports of ischemic colitis in post marketing use of Zelnorm. April 26, 2004

Cytotec Solutions, Inc. Products

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

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

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

Major Twice-A-Day 12 Hour Nasal Spray

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

Zyprexa (olanzapine)

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

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

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



Calcium Channel Blocker Overdose and New Treatment Options

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

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

Central New York Regional Poison Center

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

What immediate interventions are required for this patient?

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

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

Toxins that commonly cause bradycardia include: digoxin, organophosphates, beta receptor antagonists (BAA), non-dihydropyridine calcium channel blockers (diltiazem; verapamil) [CCB], presynaptic α_2 receptor agonists (clonidine; imidazoline derivatives), antidysrhythmics and electrolyte abnormalities. Sedative hypnotics and opioids can also cause a small decrease in heart rate. Toxins that commonly cause hypotension include: beta receptor antagonists; non-dihydropyridine calcium channel blockers; dihydropyridine calcium channel blockers (nifedipine; amlodipine); α_1 receptor antagonists (prazosin;

terazosin; phenothiazines); antidysrhythmics; tricyclic antidepressants. Sedative hypnotics and opioids can cause a small decrease in blood pressure.

Once stabilized, is there any role for gastrointestinal decontamination?

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

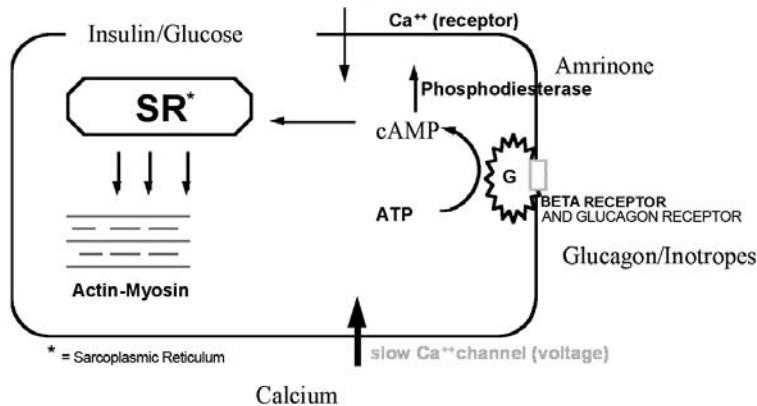
What is the typical course of CCB/BAA Poisoning?

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

Continued on page 4

the pancreas is dependent on calcium influx by a slow calcium channel. After CCB overdose, this slow calcium channel is antagonized resulting in impairment of insulin release. Laboratory examination in BAA poisoned patients may reveal hypoglycemia through a beta₂ mediated stimulation of insulin release. BAA also inhibits gluconeogenesis and glycogenolysis, which results in an impaired ability to recover from hypoglycemia.

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



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

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

Fluid:

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

Atropine:

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

Calcium:

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

Glucagon:

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

Insulin/Glucose:

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

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

Pacing:

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

Vasopressors:

Pharmacologic agents that increase and maintain perfusion may include dopamine, norepinephrine, epinephrine and dobutamine. Based on the clinical picture of toxicity, the institution of an agent with α_1 and β_1 agonist properties (eg: norepinephrine, epinephrine) is the most reasonable option. To ensure adequate optimization of therapy, invasive hemodynamic monitoring with a pulmonary artery catheter may be warranted.

Phosphodiesterase Inhibitors:

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

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

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

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

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

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

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

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

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

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

Are all CCB's the same?

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

Are all BAA's the same?

Beta-receptor antagonists competitively antagonize the effect of catecholamines at cardiac and peripheral beta-receptors. Some BAA are specific for beta₁ receptors, however; in overdose, receptor selectivity is lost. In addition to differences in receptor specificity, some BAA are lipophilic, cross the blood brain barrier and result in sedation and even seizures. Seizures after BAA toxicity should first be managed with benzodiazepines and barbiturates, if necessary. Other BAA possess a 'membrane stabilizing effect' which causes fast sodium channel blockade and manifest with QRS complex widening on the electrocardiogram. BAA with 'intrinsic sympathomimetic activity' act as partial agonists at beta receptors and may be protective in overdose.

Case Conclusion

The child was intubated for respiratory support.

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

Conclusion

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

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2. Holstege CP, Hunter Y et al. Massive Caffeine Overdose Requiring Vasopressin Infusion and Hemodialysis. *J Toxicol Clin Toxicol* 2003; 41(7): 1003-1007.
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Tox Trivia Answers ••

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

NYPC Tidbits Answers ••

- A. 2
- B. 3
- C. 1
- D. 4

SPI CORNER TOPIC: YOHIMBE

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

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

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

Yohimbine is increasing in popularity largely due to its tumescent effect. In the vascular system, however, effects are as a result of increased norepinephrine. Patients may experience significant tachycardia and hypertension. End organ manifestations are as a result of shearing forces on vessel walls and can include

central nervous system and cardiac manifestations. Additional effects that have been reported after ingestion include tremors, hyperinsulinemia, and hallucinations.

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

Select References:

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

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

TOXICOLOGY CROSSWORD POISONOUS PLANTS

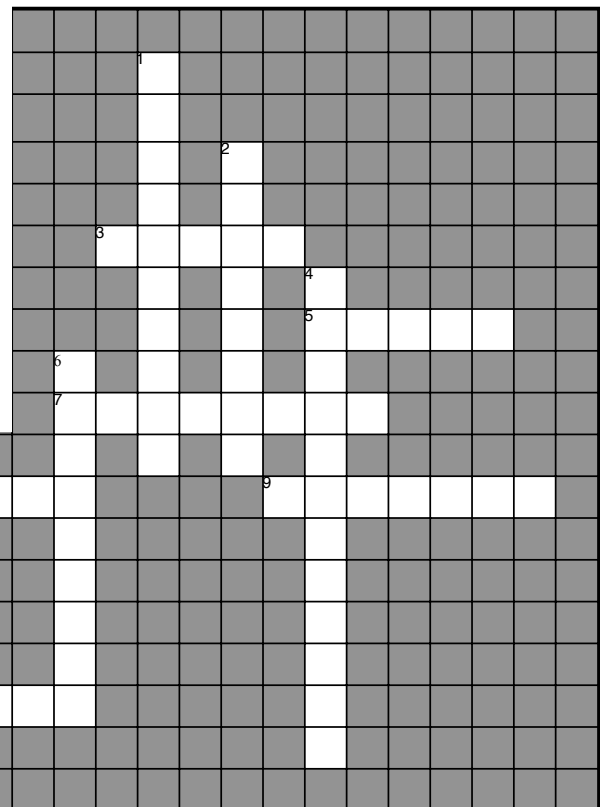
Contributed by Linda Jutton, RN, CSPI & Mary Halsey-Claps, RN, CSPI - CNY Poison Center

Down

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

Across

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



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



GNY Poison Center
750 East Adams Street
Syracuse, NY
13210