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Local Anesthetic Toxicity

Case Report:

Submitted by: Jeanna M Marraffa, Pharm.D., DABAT Upstate NY Poison Center, Syracuse, NY

An 18 month old female is found with a 30 gram tube of Dibucaine® ointment. The tube is approximately half full and partially used. After approximately 30 minutes, the child is found unresponsive and seizing. EMS is called and intubates secondary to altered mental status and continued seizure activity. Diazepam is given rectally with seizure termination. En route to the

Continued on page 4

Program Announcements • • •

Ruth A. Lawrence: Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

CNY: Our Eleventh Annual Toxicology Teaching Day will be held on November 14, 2007 at the Genesee Grand Hotel in Syracuse. Please mark your calendar!

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

LI: Pre-Registration is required. Please contact Mr. Denis Jao at 516-663-2650 to register. Both Telephone and Tele-video broadcasts will be available.

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

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

259 First Street, Mineola, Long Island, New York 11501

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

Please call administrative telephone numbers for more information.

Wednesday, January 24, 2007

TOPIC: PRINCIPLES OF ENVIRONMENTAL TOXICOLOGY

Speaker: Michael McGuigan MD, MBA

Clinical Professor of Emergency Medicine, SUNY/Stony Brook; Medical Director, Long Island Regional Poison Center at Medical Director, Winthrop University Hospital, Mineola, NY

Wednesday, February 28, 2007

TOPIC: UPDATE ON HERBAL AND DIETARY SUPPLEMENTS PRODUCTS

Speaker: Elaine Kang-Yum, R. PH., CSPI

Director of HerbWatch; Long Island Regional Poison and Drug Information Center; Winthrop University Hospital, Mineola, NY

Wednesday, March 28, 2007

TOPIC: BIOLOGICAL AGENTS AS WEAPONS OF MASS DESTRUCTION

Speaker: Robin McFee, D.O., MPH

Clinical Assistant Professor, Preventive Medicine, SUNY/Stony Brook; Consultant Toxicology Educator, Long Island Regional Poison Center at Winthrop University Hospital; Medical Director - Threat Science™/Emergistics SM US

Quinine products

FDA informed healthcare professionals and consumers that the Agency ordered firms to stop marketing unapproved drug products containing quinine, citing serious safety concerns, including deaths associated with quinine products. *December 12, 2006*

Heparin Sodium Injection

FDA notified healthcare professionals of revisions to the WARNINGS section of the prescribing information for Heparin to inform clinicians of the possibility of delayed onset of heparin-induced thrombocytopenia (HIT), a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. *October 2006*

Compounded topical anesthetic creams

FDA notified healthcare professionals and consumers about the serious public health risks related to compounded topical anesthetic creams. Exposure to high concentrations of local anesthetics, like those in compounded topical anesthetic creams, can cause grave reactions including seizures, irregular heartbeats and death. *December 05, 2006*

Dolophine (methadone hydrochloride)

FDA notified healthcare professionals of reports of death and life-threatening adverse events such as respiratory depression and cardiac arrhythmias in patients receiving methadone. *November 27, 2006*

Complete MoisturePLUS Contact Lens Care Products

FDA and Advanced Medical Optics, Inc. informed healthcare professionals and consumers of a nationwide recall of 18 lots of Complete MoisturePLUS multipurpose contact lens care solution and Active Packs distributed in the United States. Certain lots were found to have bacterial contamination which compromised sterility. *November 21, 2006*

Erythropoiesis Stimulating Agents

Procrit, Epogen, and Aranesp

FDA notified healthcare professionals of a newly published clinical study showing that patients treated with an erythropoiesis-stimulating agent (ESA) and dosed to a target hemoglobin concentration of 13.5 g/dL are at a significantly increased risk for serious and life threatening cardiovascular complications, as compared to use of the ESA to target a hemoglobin concentration of 11.3 g/dL. *November 16, 2006*

Tamiflu (oseltamivir phosphate)

Roche and FDA notified healthcare professionals of revisions to the PRECAUTIONS/Neuropsychiatric

Events and Patient Information sections of the prescribing information for Tamiflu, indicated for the treatment of uncomplicated acute illness due to influenza infection in patients 1 year and older who have been symptomatic for no more than 2 days and for the prophylaxis of influenza in patients 1 year and older. There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of Tamiflu in patients with influenza. *November 13, 2006*

Acetaminophen 500 mg Caplets by Perrigo Company

FDA and Perrigo Company notified the public of a voluntary recall of 383 lots of acetaminophen 500 mg caplets manufactured and distributed under various store-brands as a result of small metal fragments found in a small number of these caplets. *November 9, 2006*

Heartland Repack Services products

Heartland Repack Services and FDA notified healthcare professionals of a voluntary recall of all products containing a lot number beginning with "K" (example: K12345). Drugs repackaged by Heartland Repack Services are distributed through their own pharmacy services to Omnicare nursing homes and other institutional facilities. This recall was initiated because there is the potential for mislabeling and packaging mix-up. *July 27, 2006*

Effexor XR (venlafaxine HCl) Extended-Release Capsules

Effexor (venlafaxine HCl) Tablets

Wyeth and FDA notified healthcare professionals of revisions to the OVERDOSAGE/Human Experience section of the prescribing information for Effexor (venlafaxine HCl), indicated for treatment of major depressive disorder. In postmarketing experience, there have been reports of overdose with venlafaxine, occurring predominantly in combination with alcohol and/or other drugs. Published retrospective studies report that venlafaxine overdose may be associated with an increased risk of fatal outcome compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. *October 17, 2006*

Menactra (Meningococcal Conjugate Vaccine A, C, Y, and W135)

FDA and CDC updated an October 2005 alert to consumers and health care providers regarding reports of Guillain Barre Syndrome (GBS) following administration of Meningococcal Conjugate Vaccine A, C, Y, and W135, manufactured by Sanofi Pasteur. *October 20, 2006*

Continued on page 3

Roche Diagnostics CoaguChek PT Test Strips

Roche Diagnostics and FDA informed consumers and healthcare professionals of the recall of CoaguChek PT test strips used to determine blood clotting time of patients taking anti-coagulant medication to prevent blood clots. The recall was due to the potential for a test strip defect that may cause falsely elevated test results. *October 20, 2006*

Gleevec (imatinib mesylate)

Novartis and FDA notified healthcare professionals about revisions to the PRECAUTIONS section of the prescribing information, describing the occasional occurrence of severe congestive heart failure and left ventricular dysfunction in patients taking Gleevec. *October 19, 2006*

LifeScan One Touch Blood Glucose Test Strips - Counterfeit Alert

Recall classified as Class I because use of the counterfeit products could cause serious injury or death. *December 12, 2006*

Coumadin (warfarin sodium)

FDA and Bristol-Myers Squibb notified pharmacists and physicians of revisions to the labeling for Coumadin, to include a new patient Medication Guide as well as a reorganization and highlighting of the current safety information to better inform providers and patients. *October 2006*

Isotretinoin - Accutane and generic isotretinoin

FDA and the iPLEDGE program notified healthcare professionals and patients of an update to iPLEDGE, a risk management program to reduce the risk of fetal exposure to isotretinoin, that will eliminate one element of the program, the 23 day lock-out period for males and females of non-child bearing potential. *October 06, 2006*

Lamictal (lamotrigine)

The FDA notified healthcare professionals and patients of new preliminary information from the North American Antiepileptic Drug Pregnancy Registry that suggests that babies exposed to Lamictal, indicated to treat seizures and bipolar disorder, during the first three months of pregnancy may have a higher chance of being born with a cleft lip or cleft palate. *September 28, 2006*

Avastin (bevacizumab)

Genentech and FDA notified healthcare professionals about revisions to the WARNINGS and ADVERSE REACTIONS sections of the prescribing information

to inform healthcare professionals of 1] cases of a rare brain-capillary leak syndrome [reversible posterior leukoencephalopathy syndrome (RPLS)] and 2] post-marketing reports of nasal septum perforation. *September, 2006*

Ortho Evra (norelgestromin/ethinyl estradiol)

Ortho-McNeil and FDA notified healthcare professionals and patients about revisions to the prescribing information to inform them of the results of two separate epidemiology studies that evaluated the risk of developing a serious blood clot in women using Ortho Evra compared to women using a different oral contraceptive. *September 20, 2006*

Ibuprofen and Aspirin Taken Together

FDA notified consumers and healthcare professionals that taking Ibuprofen for pain relief and aspirin at the same time may interfere with the benefits of aspirin taken for the heart. *September 8, 2006*

Ellagimax Capsules, Coral Max Capsules, Coral Max without Iron Capsules, and Advanced Arthritis Support Capsules

FDA notified healthcare professionals and consumers of the seizure of Ellagimax capsules, Coral Max capsules, Coral Max without Iron capsules, and Advanced Arthritis Support capsules distributed by Advantage Nutraceuticals, LLC, because the products, labeled as dietary supplements, are being promoted to treat serious disease conditions, including but not limited to cancer, arthritis, fibromyalgia, and seizures. The products have not been shown to be safe and effective to treat these conditions. *September 06, 2006*

Human Tissues recovered by Donor Referral Services (DRS)

FDA notified healthcare professionals that human tissues recovered by Donor Referral Services (DRS) may not have met FDA requirements for donor eligibility. *August 30, 2006*

Steris Amsco Sonic Energy Cleaner and Amsco Sonic Energy Console

Steris and FDA notified hospital and long term care facility managers of a fire risk with use of Amsco Sonic Energy Cleaner and/or an Amsco Sonic Energy Console, used for cleaning reusable medical equipment. *June 21, 2006*

Alaris SE Infusion Pumps

Recall classified as Class I. The manufacturer provided recommendations to users for safe operation of the product. FDA provided Q&As. *September 26, 2006*

hospital, the patient becomes bradycardic with a heart rate of 40 beats per minute, which responds to a single dose of atropine.

On arrival to the ED, she is unresponsive to painful stimuli. Her vital signs are: blood pressure, 100/50 mmHg; heart rate, 90 beats per minute; respirations, 16 breaths per minute (on ventilator); rectal temperature, 97 F; fingerstick glucose, 214 mg/dL. Physical examination is non-contributory.

An electrocardiogram reveals AV nodal block with a QRS complex duration of 134 milliseconds, QTc duration of 554 milliseconds and transient episodes of ventricular tachycardia.

What is Dibucaine®?

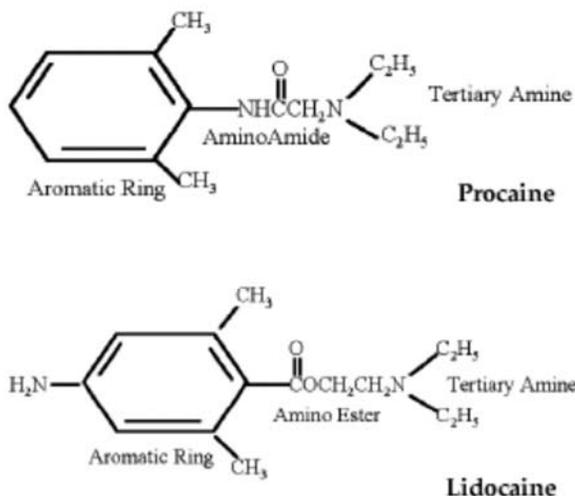
Dibucaine is an over the counter local anesthetic of the amino amide class. The major toxicity of local anesthetics includes the central nervous (CNS) and cardiovascular system. Local anesthetics fall into two chemically distinct groups: the amino amides and the amino esters.

Table: Classification of Local Anesthetics

Amino Esters	Maximum Dose	Amino Amides	Maximum Dose
Procaine	7 mg/kg	Lidocaine	4.5 mg/kg
Benzocaine		Mepivacaine	7 mg/kg
Chlorprocaine	11 mg/kg	Prilocaine	6.6-8.8 mg/kg
Tetracaine	2.5 mg/kg	Bupivacaine	2 mg/kg
Cocaine	1-3 mg/kg	Ropivacaine	
		Dibucaine	

All local anesthetics have an aromatic structural ring connected by an ester or amide linkage which is bound to a hydrophilic amine.

Figure: Structural differences of local anesthetics: Amide vs. Ester



Dibucaine is a potent, long-acting agent that is no longer available for systemic use in the United States due to its toxicity profile. It is currently available over the counter as a 0.5 % and 1% ointment and cream.

Dibucaine is considered one of the most potent and toxic amide anesthetics. (Kasaba et al; Dayan et al). Kasaba et al. evaluated the neurotoxicity of multiple agents including lidocaine, bupivacaine, tetracaine, dibucaine and mepivacaine. They demonstrated that the degree of neurotoxicity was procaine = mepivacaine < ropivacaine = bupivacaine < lidocaine < tetracaine < dibucaine. Dibucaine is 25 times more neurotoxic than procaine and five times more neurotoxic than lidocaine. With all of the amide anesthetics, the dose to produce CNS toxicity is lower than that which causes cardiac toxicity.

Despite this, the toxic and fatal dose of dibucaine is less well-defined. One child died after ingestion of only 0.8 mg/kg. (McClenahan et al) In the most recent literature, Dayan et al. described 3 patients that ingested between 15 and 19 mg/kg of dibucaine ointment with fatal outcomes. We estimate our patient ingested 12 – 13 mg/kg.

What are the toxic effects and the mechanism of toxicity associated with dibucaine and related local anesthetics?

Major toxicity associated with local anesthetics includes central nervous system (CNS) and cardiotoxic effects. Toxicity typically occurs when either a toxic dose is administered, a therapeutic dose given too quickly or a when a therapeutic dose is given either directly into a blood vessel or through a mucous membrane causing high local concentrations.

CNS toxicity typically is manifested by headache, drowsiness, lightheadedness, shivering, tremors, seizures and/or coma. These effects are Occur through selective inhibition of fast sodium channels and inhibition of γ -aminobutyric acid (GABA) in cortical cerebral inhibitory pathways causing unopposed excitatory activity.

Cardiotoxicity is typically manifested by bradycardia, hypotension, myocardial depression, ventricular dysrhythmias including widening of the QRS complex duration and/or cardiac arrest. Toxicity occurs secondary to blockade of the fast sodium channels in the heart, which results in a slowing of myocardial automaticity, cardiac conduction and rate of spontaneous depolarization. They also directly decrease myocardial

contractility. Bupivacaine has the highest potential to cause cardiotoxicity due to its high lipid solubility and its slow dissociation from binding sites on the inactive sodium channel. The majority of the data and treatment recommendations for local anesthetic induced cardiotoxicity are based on the bupivacaine toxic patient. In addition, these agents are inducers of oxidative stress, which sometimes results in methemoglobinemia.

What is Methemoglobinemia, when does it present and how is it treated?

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. 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 symptomatic drug-induced methemoglobinemia is intravenous methylene blue (1-2mg/kg), which after conversion to leukomethylene blue by nicotinamide adenine nucleotide phosphate (NADPH) is able to reduce iron on hemoglobin to the ferrous form.

How is local anesthetic toxicity treated?

Treatment of CNS toxicity is generally supportive with careful attention to airway, breathing and circulation.

Seizures should be treated using intravenous benzodiazepines such as lorazepam (1-2 mg boluses) or diazepam (5-10 mg boluses). If seizures continue despite adequate therapy with benzodiazepines, second line agents should be considered including barbiturates, general anesthetics or propofol. These agents will likely cause seizure termination; however, it is essential to maintain the airway due to the degree of respiratory depression they cause. Propofol can cause bradycardia and perhaps may worsen the degree of

bradycardia in the setting of local anesthetic cardiac toxicity and therefore, should be used with caution and not as first-line therapy.

Once cardiovascular toxicity occurs, it is often difficult to manage and should be treated aggressively. Cardiovascular collapse is secondary to decreased vascular tone, decreased inotropy and ventricular dysrhythmias induced by local anesthetics. Standard advanced cardiac life support (ACLS) protocols should be implemented when dealing with the majority of local anesthetic induced cardiac toxicity. 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.

Dysrhythmias are often refractory to standard interventions including pharmacologic therapy. The use of sodium bicarbonate provides theoretical benefit due to the mechanism of fast sodium channel blockade by local anesthetics resulting in conduction abnormalities including widening of the QRS complex duration by slowing ventricular depolarization.

Sodium bicarbonate provides a sodium load and overwhelms the blocked sodium channels in the myocardium with a resultant narrowing of the QRS complex. The use of sodium bicarbonate for other drug induced causes of widened QRS

complexes, such as with tricyclic antidepressants, is well known. There is minimal data with the use of sodium bicarbonate in local anesthetic toxicity however, should be considered in a patient with a wide QRS complex duration.

Lidocaine, a Class Ib anti-dysrhythmic, has also been used in the setting of cardiovascular toxicity secondary to local anesthetics, particularly in the setting of bupivacaine toxicity. Lidocaine competes for the cardiac sodium channel and at high doses, and may theoretically displace the local anesthetic from the cardiac sodium channel. Lidocaine and other Class Ib drugs cause inhibition of the sodium channel by binding to the inactive channels and have rapid 'on-off' kinetics to the sodium channels. Because they bind to inactive sodium channels, Class Ib agents have no effect on the rate of phase 0 or depolarization of the action potential. Conversely, local anesthetics, including dibucaine,



are Class Ia sodium channel blockers and have highest affinity for open sodium channels and slow the rate of phase 0 of the action potential and delay ventricular depolarization. The differences in these two classes leads to the theoretical benefit of lidocaine in local anesthetic toxicity due to it competing for the sodium channels and perhaps be beneficial. However, lidocaine may exacerbate the CNS and cardiovascular toxicity of other local anesthetics and should not be routinely used.

Serious cardiotoxicity from local anesthetics results in a high degree of morbidity and mortality. Despite aggressive care, often times, the cardiovascular collapse and shock are refractory. The most promising approach to treating bupivacaine-induced cardiotoxicity is the use of a 20% lipid emulsion infusion. There is only a single human case report of the use of a 20% lipid infusion for bupivacaine related cardiac arrest. A 58 year old male experienced bupivacaine-induced cardiac arrest and failed treatment with epinephrine, atropine, amiodarone and vasopressin. After initiation of a 100 mL bolus followed by 0.5 mL/kg/min of 20% lipid emulsion, the patient was successfully resuscitated. (Rosenblatt et al) Weinberg et al. studied the effects of a 4ml/kg bolus injection of 20% lipid emulsion followed by an infusion of 0.5 mL/kg/min versus saline in dogs given bupivacaine 10 mg/kg. All 6 dogs in the control died compared to survival of all 6 dogs in the lipid group. (Weinberg et al) The mechanism for this effect remains unknown although Weinberg et al. hypothesize that the lipid infusion creates a lipid plasma phase that is able to extract the lipid soluble bupivacaine out of tissue sites. Potential adverse events of lipid emulsions include hypertriglyceridemia and pancreatitis.

Though only successfully used in a single human case report, the use of lipid infusions appears as a promising treatment modality for bupivacaine-induced cardiotoxicity. Further research in this area is critical; however, we propose to consider the use of lipid infusion in the patient with severe, refractory cardiovascular collapse, as few alternatives exist.

There is very little data regarding dibucaine toxicity and based on previous case series and animal data, it is significantly more toxic than other readily available local anesthetics. Due to its relative ease of availability, as an over the counter product, we urge health care providers to provide education to the risk of this highly toxic over the counter preparation and report any adverse events/toxicity to the FDA's Medwatch program.

Patient Follow-Up

The patient was given 1mEq/kg sodium bicarbonate bolus followed by a sodium bicarbonate infusion with narrowing of the QRS complex duration. IV fluids were initiated for hypotension.

After the administration of sodium bicarbonate, repeat vital signs include heart rate 100 bpm and blood pressure 103/50 mmHg.

She remained in normal sinus rhythm with narrow QRS complex duration and 12 hours after presentation, was extubated and recovered without sequelae.

Selected References

1. Kasaba T, Onizuka S, Takasaki M. Procaine and Mepivacaine have less toxicity in vitro than other clinically used local anesthetics. *Anesth Analg* 2003; 97:85-90.
2. Gunter JB. Benefit and Risks of Local Anesthetics in Infants and Children. *Pediatr Drugs* 2002; 4(10):649-672.
3. Dayan PS, Litovitz TL, Insley Crouch B, Scalzo AJ, Klein BL. Fatal Accidental Dibucaine Poisoning in Children. *Ann Emerg Med* 1996; 28:442-445.
4. Weinberg G, Ripper R, Feinstein DL, Hoffman W. Lipid Emulsion Rescues Dogs from Bupivacaine-Induced Cardiac Toxicity. *Reg Anesth Pain Med* 2003; 28(3): 198-202.
5. Rosenblatt MA, Abel M, Fischer GW, Itzkovich CJ, Eisenkraft JB. Successful Use of a 20% Lipid Emulsion to Resuscitate a Patient after a Presumed Bupivacaine-related Cardiac Arrest. *Anesthesiology* 2006; 105:217-218.
6. Weinberg G, Hertz P, Newman J: Lipid, not propofol, treats bupivacaine overdose (letter). *Anesth Analg* 2004; 99:1875.
7. Weinberg G: Reply to Drs. Goor, Groban and Butterworth-Lipid Rescue: Caveats and recommendations for the 'silver bullet' (letter). *Reg Anesth Pain Med* 2004; 29:74-5.

SPI CORNER: DEXTROMETHORPHAN

Contributed by: Laureene Piwinski, RN, CSPI, Upstate NY Poison Center

Dextromethorphan(DM) is generally regarded as a safe and effective antitussive. It is the optical isomer of levopropyl, an opioid analgesic, but it has no analgesic properties.

DM is commonly abused by Teen and Tweens due to ease of access. In most cases, toxicity does not develop and patients, however, significant toxicity can occur

after large doses and after use of products containing multiple agents. We receive many calls from hospital emergency departments after abuse of DM. DM is available in cough and cold medications over the counter and not regulated. Common street names for DM are Dex, Robo, DMX, skittles, syrup, triple C. The terms for being high on DM are Robo-tripping, or skittling.

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Contributed by: Jamie Nelsen, Pharm.D.

Question: Is there a benefit to using NaHCO₃ rather than NS for prevention of ARF secondary to rhabdomyolysis?

Background:

A 28 YOM was initially found extremely agitated due to unknown cause. In the ED he required intubation and sedation. His CK initially was 9073, increased to >30,000 within six hours and peaked at 565,625. He is receiving hydration with sodium bicarbonate solution, 250 cc/hr. His CKs are now <200,000.

Answer:

Rhabdomyolysis literally translates from striated (rhabdo) muscle (myo) lysis (breakdown). Rhabdomyolysis can occur as a result of both traumatic and atraumatic insults (heat stroke, seizures, drugs, etc). Common clinical findings of rhabdomyolysis include elevations in creatinine kinase (CK), aminotransferases and potassium, and the presence of myoglobin in the serum and urine.

The goal of management is to prevent the progression to renal failure. Renal failure secondary to myoglobinuria has been attributed to three distinct processes: renal vasoconstriction, formation of casts and direct cytotoxicity.² In an acidic environment myoglobin dissociates into globin and ferriheme, which is tubulotoxic, possibly as a result of production of oxygen free radicals.¹ The cornerstones of therapy are threefold: 1) correction of hypovolemia 2) enhance the clearance of hem proteins from the circulation and the kidney, and 3) mitigate the direct adverse consequences of heme proteins on the proximal tubular epithelium.² Aggressive hydration, regardless of the agent used, fulfills the first two criteria, and may cause a dilutional alkalinization of the urine, although the degree of alkalinization may be insufficient in severe cases. In those instances, more aggressive alalinization with sodium bicarbonate solution in theory may better facilitate the prevention of cytotoxicity by increasing the solubility of myoglobin and reducing the dissociation of ferihemate.¹

The importance of early aggressive hydration was illustrated in two earlier observational reports involving patients hospitalized with extensive crush injuries.³ The two groups consisted of 15 men with roughly the same degree of injury. The seven men in the first group (1979) received hydration at least six hours after extrication. In every member of this group, acute

renal failure developed despite aggressive hydration thereafter. The outcomes of this group were compared to a second group of seven men (1982) who received hydration prior to extrication, followed by alkalinization therapy upon hospital admission. None of these patients developed renal failure. An eighth member of the second group however had hydration accidentally delayed for 24 hours, during which time he received minimal fluids (2L). He required hemodialysis for one month. The stark contrast in outcomes between these two groups highlighted the importance of aggressive hydration, although it remained unclear if alkalinization was truly advantageous.

This issue was addressed in a recent retrospective study serially evaluating all trauma admissions over five years for the development of renal failure secondary to rhabdomyolysis.⁴ Abnormal CK was found in 1,771 patients, with 10% of patients developing renal failure (Scr >2.0 mg/dL). The risk for renal failure significantly increased at a CK threshold of > 5,000 U/L (p < 0.0001), with increasing risk with as CK rises from 5,000 to >30,000 (OR 2.4 to 8.0). When subjects were stratified based on CK levels, in patients with CK levels from 5,000—30,000 U/L, alkalinization did not reduce the risk of renal failure, dialysis, or mortality. In patient with CK > 30,000 U/L however, there was a trend toward improved outcome. The authors acknowledge the lack of significance may have been attributable to the small sample size.

In summary, early and aggressive hydration should be instituted if rhabdomyolysis is suspected. Based on lack of strong prospective data, aggressive hydration with normal saline to keep urine flow 200—300 cc/hr is likely to be adequate in most patients. If it is not possible to maintain a urinary pH > 6.0,1 alkalinization with bicarbonate may be beneficial, particularly in patients with CK values > 30,000 U/mL. If patients are alkalinized, patients should be monitored closely for hypokalemia and potassium supplements administered as necessary.

References

1. Wax, PM. *Antidotes In Depth: Sodium Bicarbonate*. In: *Goldfrank's Toxicologic Emergencies*. 2002.
1. Available: <http://online.statref.com>. Accessed: 3/06.
2. *Kidney International*. 1996;49:314-26
3. *NEJM*. 1990; 322(12):825-8.
4. *J Trauma*. 1994; 56(6):1191-6.

SPI CORNER: DEXTROMETHORPHAN

Continued from page 6

Although structurally similar to opioids, toxic effects after large doses (5-10 times the therapeutic dose) are thought to occur through NMDA inhibition and are similar to those seen after ketamine and phencyclidine use. Symptoms include euphoria, disorientation, depersonalization, CNS depression or agitation, impaired coordination, dystonic reactions, nystagmus, visual hallucinations, and dissociative anesthesia. Vital sign changes can include tachycardia, hypertension, and respiratory depression. Serotonin syndrome may also be evoked in patients concurrently on other serotonergic agents such as antidepressants and MAOIs. Due to its structural similarity, DM is often noted to cause a false positive on qualitative phencyclidine drug testing.

Dextrophan, the active metabolite of DM, is produced by the enzyme CYP2D6 which has genetic polymorphisms among different populations. Extensive metabolizers experience more of the sought after euphoria producing psychoactive effects, while poor

metabolizers suffer more of the adverse effect such as dysphoria, and psychomotor impairment. Individual responses and abuse tendencies can vary greatly due to the variances in metabolism.

Treatment for dextromethorphan toxicity is symptomatic and supportive. Benzodiazepines are indicated for agitation and dysphoria, tachycardia and hypertension. Because of the combination cough and cold preparations that are available over-the-counter, symptoms of toxicity may be mixed with anticholinergic toxicity (warm, dry, flushed skin, mydriasis, and tachycardia) from antihistamines, and more pronounced by sympathomimetic effects (CNS stimulation, hypertension) if there is pseudoephedrine in the product. Many combination products also contain acetaminophen, so a level should be obtained in all DM ingestions. N-acetylcysteine (Mucomyst®) should be initiated if the time of exposure is greater than 8 hours prior to presentation or unknown and continued until acetaminophen toxicity is ruled out.





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Location: New Life Conference Rooms B&C
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259 First Street, Mineola, Long Island, New York 11501
Times for ALL Conferences are: 12:15 PM-1:45 PM

April 24, 2007

TOPIC: RADIOLOGICAL AGENTS AS WEAPONS OF MASS DESTRUCTION

Speaker: David Gregorius, MS, DABSNM, DABR

May 29, 2007

TOPIC: CHEMICAL AGENTS AS WEAPONS OF MASS DESTRUCTION

Speaker: Robin McFee, DO, MPH

June 12, 2007

TOPIC: TOXIC MYSTERY CASES

Speaker: Kathy Ferguson, DO

Antidotes: How Much is Enough?

Case Report:

Submitted by: John G. Benitez, MD, MPH, Director, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

What? Hospitals don't have enough antidotes to treat overdosed patients? As the case presentations in this issue show, on occasion, hospitals either don't have any or don't have enough antidotes to treat a patient. How much is enough? Depending on the resources available at a given hospital they should have enough to at least stabilize one or more patients, and enough to continue the treatment during transport to a tertiary care center if necessary. If they are going to keep the patient in-house, then they should have enough antidote (or the availability to obtain rapidly) to treat for as long as is necessary.

Surveys done since the late 1990's show that many hospitals in the US and Canada do not keep an adequate antidote supply (for some types of overdoses) to properly care for a patient. This occurs in large urban hospitals and in small rural ones as well. In a study from British Columbia (BC) only 8.9% of hospitals had all 21 recommended antidotes (as recommended by BC).¹ In a similar survey in Colorado, Wyoming and Nevada, the investigators looked at 8 key antidotes to treat one 70 kg patient. The median

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716.878.7871 • <http://wnypoison.org>

Ruth A. Lawrence NY Poison Center (FL)

585.273.4155 • www.FingerLakesPoison.org

Upstate New York Poison Center (UNY)

315.464.7078 • www.upstatepoison.org

New York City Poison Control Center (NYC)

212.447.8152

Long Island Poison & Drug Info Center (LI)

516.663.4574 • www.LIRPDIC.org

Please call administrative telephone numbers for more information.

V.MAX supplement product

Barodon SF and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of a supplement product sold under the name V.MAX. FDA advised that this poses a threat to consumers because Aminotadalafil may interact with nitrates found in some prescription drugs (such as nitroglycerin) and may lower blood pressure to dangerous levels. *March 15, 2007*

Rhino Max (Rhino V Max) supplement product

Cosmos Trading, Inc. and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of a supplement product sold under the name Rhino Max (Rhino V Max) in 5-tablet boxes or 15-tablet boxes. Lab analysis by FDA of product samples found the product contains Aminotadalafil, an analogue of Tadalafil, an FDA-approved drug used to treat Erectile Dysfunction (ED). *March 16, 2007*

Zyvox (linezolid)

FDA notified healthcare professionals of new emerging safety concerns about Zyvox (linezolid) from a recent clinical study. This open-label, randomized trial compared linezolid to vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections including those with catheter-site infections. Patients treated with linezolid had a higher chance of death than did patients treated with any comparator antibiotic, and the chance of death was related to the type of organism causing the infection. Mortality was higher in patients treated with linezolid who were infected with Gram negative organisms alone, with both Gram positive and Gram negative organisms, or who had no infection when they entered the study. *March 16, 2007*

Sedative-hypnotic drug products

FDA notified healthcare professionals of its request that all manufacturers of sedative-hypnotic drug products, a class of drugs used to induce and/or maintain sleep, strengthen their product labeling to include stronger language concerning potential risks. These risks include severe allergic reactions and complex sleep-related behaviors, which may include sleep-driving. *March 14, 2007*

Actimmune (Interferon Gamma 1-b)

FDA notified healthcare professionals of the early termination of the INSPIRE clinical study of Actimmune for idiopathic pulmonary fibrosis (IPF). The study was stopped because an interim analysis showed that patients with IPF who received Actimmune did not benefit. *March 09, 2007*

Actos (pioglitazone) Tablets

ACTOplus met (pioglitazone and metformin hydrochloride) Tablets

Duetact (pioglitazone and glimepiride) Tablets

Takeda and FDA notified healthcare professionals of recent safety data concerning pioglitazone-containing products. The results of an analysis of the manufacturer's clinical trial database of pioglitazone showed more reports of fractures in female patients taking pioglitazone than those

taking a comparator (either placebo or active). *March 2007*

Gebauer Salivart Oral Moisturizer

The Gebauer Company notified healthcare professionals and consumers of a nationwide recall of certain lots of Salivart Oral Moisturizer. The recall was initiated because some lots do not meet the Company's internal specification for aerobic microorganisms and mold. *March 01, 2007*

Ergotamine tartrate

FDA informed healthcare professionals and consumers that the Agency ordered twenty firms to stop marketing unapproved drug products containing ergotamine tartrate. *March 01, 2007*

Baraclude (entecavir) Tablets and Oral Solution

FDA and Bristol-Myers Squibb notified healthcare professionals of revisions to the MICROBIOLOGY/Antiviral Activity and INDICATIONS AND USAGE/Description of Clinical Studies/Special Populations sections of the prescribing information for Baraclude. The revised labeling is the result of a case report in which a human immunodeficiency virus (HIV) variant containing the M184V resistance substitution was documented during Baraclude treatment for chronic hepatitis B virus (HBV) infection in an HIV/HBV co-infected patient who was not simultaneously receiving highly active antiretroviral therapy (HAART). *February 2007*

CellCept (mycophenolate mofetil)

Roche and FDA notified cardiac transplant healthcare practitioners about a clinical study (Heart Spare The Nephron) that was terminated due to an observed increased incidence of grade IIIA acute rejection in heart transplant patients switched from calcineurin inhibitor and CellCept to Rapamune (sirolimus) and CellCept at 12 weeks post heart transplantation. *February 2007*

Attention Deficit Hyperactivity Disorder (ADHD) drug products

FDA notified healthcare professionals that the manufacturers of all drug products approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) have been directed to develop Patient Medication Guides to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines and to advise them of precautions that can be taken. *February 21, 2007*

Xolair (omalizumab)

FDA notified asthmatic patients and healthcare professionals of new reports of serious and life-threatening allergic reactions (anaphylaxis) in patients after treatment with Xolair (omalizumab). *February 21, 2007*

Avandia (rosiglitazone maleate)

Avandamet (rosiglitazone maleate and metformin hydrochloride)

Avandaryl (rosiglitazone maleate and glimepiride)

Glaxo SmithKline (GSK) notified healthcare professionals of the results of a randomized, double-blind parallel group

Continued on page 3

study [ADOPT] of 4,360 patients with recently diagnosed type 2 diabetes mellitus followed for 4-6 years to compare glycemic control with rosiglitazone relative to metformin and glyburide monotherapies. Significantly more female patients who received rosiglitazone experienced fractures of the upper arm, hand, or foot, than did female patients who received either metformin or glyburide. *February 2007*

Unsafe, Misrepresented Drugs Purchased Over the Internet:

Ambien (zolpidem tartrate), Xanax (alprazolam), Lexapro (escitalopram oxalate), and Ativan (lorazepam)

FDA informed consumers and healthcare professionals regarding the possible dangers of buying prescription medications online. Individuals who ordered Ambien, Xanax, Lexapro, and Ativan over the internet received a product that contained haloperidol, a powerful anti-psychotic drug. *February 16, 2007*

Erythropoiesis Stimulating Agents:

Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa)

FDA notified healthcare professionals of new safety information for erythropoiesis-stimulating agents (ESAs) Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa). Four new studies in patients with cancer found a higher chance of serious and life-threatening side effects or death with the use of ESAs. These research studies were evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA. *March 09, 2007*

Rotavirus, Live, Oral, Pentavalent vaccine (RotaTeq)

FDA issued a Public Health Notification to inform health care providers and consumers about 28 post-marketing reports of intussusception following administration of Rotavirus, Live, Oral, Pentavalent vaccine (RotaTeq). *February 13, 2007*

Ketek (telithromycin)

FDA and Sanofi-Aventis notified healthcare professionals of revisions to the prescribing information, including a BOXED WARNING and a new Patient Medication Guide, for the antibiotic Ketek. Two of the three previously approved indications, acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis, were removed from the prescribing information because the balance of benefits and risks no longer support approval of the drug for these indications.

Heparin Sodium Injection 10,000 units/mL, and HEP-LOCK U/P 10 units/mL Medication Errors

Baxter and FDA notified healthcare professionals of the potential for life threatening medication errors involving two Heparin products, Heparin Sodium Injection 10,000 units/mL, and HEP-LOCK U/P 10 units/mL. *February 06, 2007*

Topical Anesthetic Drugs for Cosmetic Procedures

FDA informed consumers and healthcare professionals of the potential hazards of using skin numbing products containing topical anesthetic drugs such as lidocaine, tetracaine, benzocaine, and prilocaine in a cream, ointment, or gel. Without supervision, a patient may apply large amounts of the numbing product to their skin, which can cause life-threatening side effects and death. *February 06, 2007*

Lucentis (ranibizumab injection)

Genentech informed healthcare professionals of preliminary safety information from a planned interim analysis in an ongoing study (SAILOR) which confirmed the higher incidence of stroke in the 0.5 mg dose group compared to the 0.3 mg dose group (1.2% versus 0.3%, respectively; P=0.02) of patients with neovascular (wet) age-related macular degeneration who received intravitreal Lucentis. *January 24, 2007*

Aranesp (darbepoetin alfa)

Amgen notified the oncology medical community of the results of a large, multicenter, randomized, placebo-controlled study showing that Aranesp was ineffective in reducing red blood cell transfusions or fatigue in patients with cancer who have anemia that is not due to concurrent chemotherapy. *January 26, 2007*

Liviro3 Dietary Supplement Recall

FDA and Ebek, Inc. notified healthcare professionals and consumers of a voluntary nationwide recall of the company's dietary supplement because the product contains tadalafil, a drug used to treat erectile dysfunction. *January 19, 2007*

Cough and Cold Medications in Children Less Than Two Years of Age

The Centers for Disease Control and Prevention (CDC) issued a Morbidity and Mortality Weekly Report (MMWR) article describing three deaths in U.S. infants aged less than 12 months associated with cough and cold medications. These medications were determined by medical examiners or coroners to be the underlying cause of death. The cases described in this report underscore the need for clinicians to use caution when prescribing and caregivers to use caution when administering cough and cold medications to children aged less than 2 years. *January 12, 2007*

Tamiflu (oseltamivir phosphate)

Roche notified healthcare professionals of a correction to a Dear Healthcare professional letter issued on November 13, 2006. The original letter referenced changes to the PRECAUTIONS Section of prescribing information for Tamiflu about post marketing reports of self-injury and delirium with the use of Tamiflu in patients with influenza. The prescribing information that accompanied the letter contained an incorrect dosing chart for the Standard Dosage of Tamiflu Oral Suspension for prophylaxis of influenza in pediatric patients. *December 26, 2006*

Antidotes: How Much is Enough?

Continued from page 1

number of stocked antidotes was only 50% of the identified key antidotes! Independent predictors for inadequate stock were small rural hospital and not having a formal review process for antidote stocking.² Similarly, only 10% of hospitals in Massachusetts carried 14 of the recommended antidotes to treat one adult (70 kg) patient.³ Similar problems with antidote stocking rates were found in Ontario and Quebec, Canada.^{4,5}

A consensus multidisciplinary panel reviewed available evidence on multiple antidotes and published their results in 2000.⁶ Four key questions were asked by the panel: 1) Is the antidote effective?, 2) Is the antidote needed within 1 hour of patient presentation to prevent major morbidity or death?, 3) How many patients should a facility prepare for?, and 4) What amount of the antidote is needed to treat a 70-kg patient? (An initial 4-hour treatment period was selected by the panel.) An antidote was considered essential for stocking if the first two questions were answered affirmatively. Twenty antidotes were evaluated by the panel; SIXTEEN were recognized as being essential and recommended to be *stocked by any facility* that accepts emergency patients. A modified table of these 16 antidotes, along with recommended stocking amounts, appears below. The total estimated cost for stocking these antidotes in adequate amounts was estimated at \$19,809. Approximately half of the cost

was associated with digoxin immune Fab fragments, which most hospital do have. The next most expensive antidotes were crotalid antivenin (\$4,504), fomepizole (\$2,400) and glucagon (\$1,922). In areas where these poisonings or envenomations occur, even if only once per year, these critical stocks need to be maintained. In the case of fomepizole, ethanol, an alternative therapy, has a cheaper acquisition cost, but also requires the availability of a pharmacist to prepare the appropriate solution in a timely fashion, more aggressive therapeutic drug monitoring, and may be associated with untoward effects.

Since the panel looked at what antidotes are REQUIRED WITHIN ONE HOUR to prevent major morbidity or mortality, there is no time to transfer the patient or to request these antidotes from elsewhere. Each facility can determine how best to meet these needs. Some facilities are tertiary care centers and should have higher levels of stocking in anticipation of local cases and cases transferred in from the region. Some facilities have developed special areas in their pharmacy so the location of critical antidotes may be found in a timely fashion and others have developed a special "antidote cart".^{6,7} Again, the numbers above reflect the minimum amount of antidotes ANY facility should have.

What does your pharmacy stock? How does your pharmacy decide what to stock? Become involved in the process

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Recommended Antidotes and Stocking Amounts

Antidote	Indication	No. of patients	Dose (70 kg)	Total stocking amount
Acetylcysteine	Acetaminophen	2	19.6 grams	39.2 grams
Antivenin (crotalid)	Crotalid snakes (rattlesnake)	1	10 vials	10 vials
Atropine sulfate	Carbamate or organophosphate insecticide or nerve agent	2	75 milligrams	150 mg
Calcium gluconate and chloride	Hydrogen fluoride (HF) or calcium channel blocker	2	100 mEq	200 mEq
Cyanide kit	Cyanide	2	1 kit	2 kits
Deferoxamine	Iron	1	8.4 grams	8.4 grams
Digoxin immune Fab	Digoxin, digitoxin or natural products containing cardiac glycosides (plants, toads)	1	15 vials	15 vials
Dimercaprol (BAL)	Acute arsenic, inorganic mercury or lead (encephalopathy)	1	280 milligrams	280 mg
Ethanol (100%)	Methanol or ethylene glycol	2	90.7 milliliters	181.4 mL absolute alcohol
Fomepizole	Methanol or ethylene glycol	2	1.05 grams	2.1 grams
Glucagon	b-adrenergic blocker or calcium channel blocker	1	50 milligrams	50 mg
Methylene blue	Methemoglobinemia	2	140 milligrams	280 mg
Naloxone	Opioids	2	15 milligrams	30 mg
Pralidoxime (PAM)	Organophosphate insecticides, nerve agents	2	1 gram	2 grams
Pyridoxine	Isoniazid (INH)	1	10 grams	10 grams
Sodium bicarbonate	Tricyclic antidepressant, cocaine or salicylates	1	500 mEq	500 mEq

Antidotes: How Much is Enough?

Continued from page 4

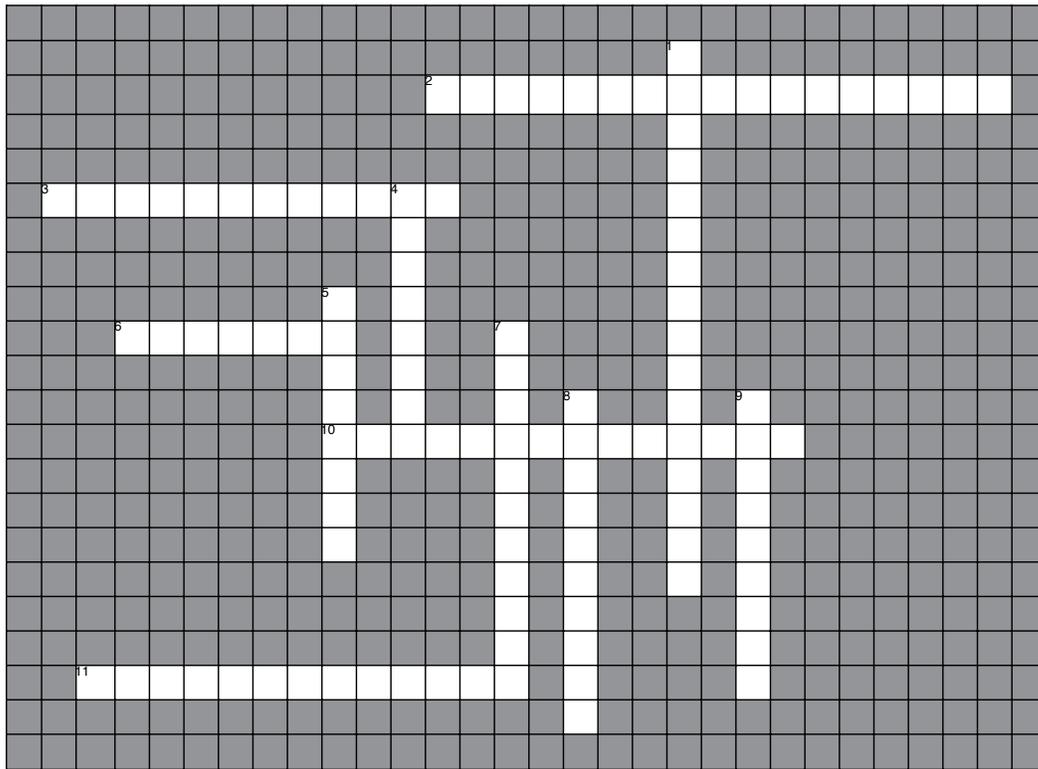
so appropriate decisions are made. Please call your poison center to discuss appropriate antidote stocking. We would be happy to discuss antidote stocking: the what, how much and even when to use. We are willing to evaluate your antidote stocks, and even meet with your pharmacy and therapeutics committee to help you out. In the near future, we will also have a poster available for your facility that describes some key antidotes, their indications and dosages. You can always reach your poison center at 1-800-222-1222.

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TOXICOLOGY CROSSWORD RECOMMENDED ANTIDOTES



WORD BANK

Sodium Bicarbonate
Acetylcysteine
Pyridoxine
Antivenin
Pralidoxime
Deferoxamine
Naloxone
Digoxin Immune Fab
Glucagon
Ethanol
Methylene Blue

ACROSS

2. This antidote is essential for treatment of cocaine or salicylate exposure.
3. A significant iron ingestion may require this antidote.
6. This antidote is needed to treat a methanol or ethylene glycol exposure.
10. ____ is used for the treatment of acetaminophen poisoning.
11. This antidote should be utilized for a patient with clinically significant methemoglobinemia.

DOWN

1. 15 vials are recommended when determining stock amounts.
4. This antidote is used for treatment of an opioid exposure.
5. ____ is used as a calcium channel blocker.
7. This antidote is the second antidote used for organophosphate insecticide or nerve agents.
8. 5 grams of ____ would treat one patient with an unknown dose of isoniazid exposure.
9. 10 vials of this antidote is the minimum recommended amount to stock for a rattlesnake bite exposure.

SPI CORNER: ANTIDOTE CASES

Antidote Shortages: Isoniazid Toxicity

Contributed by: Gina Rowan, RN, BSN, SPI, Poison Specialist, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

Case Report:

A 42-year-old female ingested an unknown amount of 300 mg tablets of isoniazid (INH) in a suicide attempt after reportedly being depressed by her father's recent death. Her roommate found an empty 30-tablet isoniazid bottle that had been filled in 2003.

Shortly before arrival to the emergency department (ED) via EMS, the patient had a seizure which quickly resolved following a single dose of diazepam. She was somnolent and incoherent, mumbling her words upon arrival. Her initial vital signs included a blood pressure of 123/54 mm/Hg, pulse rate of 127 beats per minute, respirations of 18 breaths per minute, oral temperature of 36.6° C, and an oxygen saturation level of 97% on room air. Her physical exam findings, including lungs, abdomen and extremities were normal, and a subsequent computed tomographic scan of her head and cervical spine demonstrated no acute injury.

The Poison Control Center (PCC) was contacted and the following information was advised: administer the amount of pyridoxine equivalent to the estimated amount of INH ingested. If the amount of INH ingested is unknown, administer 5 grams of pyridoxine IV at approximately 0.5 grams per minute until the seizures stop or the maximum dose has been reached.¹ The dose may be repeated if seizures do not terminate. The administration of a benzodiazepine should be used in conjunction with the pyridoxine in an attempt to achieve synergistic control of the seizures.¹ The hospital pharmacy only had a total of 3.6 grams of IV pyridoxine, an insufficient amount anticipated to be adequate for effective management.

Case Conclusion:

A subsequent call from the ED physician revealed that the patient had tolerated her pyridoxine and was more awake and able to state that she had ingested fourteen 300 mg tablets (a total of 4.2 grams). She was kept on seizure precautions without any recurrent seizure activity or the need for additional pyridoxine. She was medically cleared and admitted to psychiatric services the following day.

What could have been done if additional pyridoxine was needed? There is no antidote substitute for INH induced seizures. The best way to administer pyridoxine in a patient following in this scenario is unknown. Oral pyridoxine is 50% absorbed within 20 minutes of ingestion.^{1,2} If IV access cannot be established or if IV pyridoxine is not available, a reasonable second approach would be to crush oral pyridoxine tablets and administer them via an NG tube. If oral pyridoxine is not available in the hospital pharmacy, obtaining outside sources of this supplement is the next reasonable alternative.

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One Strike, You're Out!

Contributed by: Paul Dengler, SPI, CPNP, Poison Specialist, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

Case Report:

A 12 year old boy presents to the emergency department with his mother stating he was bitten by a water moccasin (*Crotalinae*) 30 minutes ago. No one saw the snake; the child was walking through a grassy field at time of the strike. Two punctures marks are visible and measure 14 mm apart. The child is alert, oriented and denies pain. His vital signs are stable. The wound is clean and dry without any visible swelling. What is your next step? Do you give antivenom (*Crotaline* and *Elapid*)? Your hospital has 3 vials of antivenom (*Antivenin, Crotalidae Polyvalent Immune Fab*). Is this enough?

The major indications for crotaline antivenom therapy are: 1) rapid progression of swelling, 2) significant coagulopathy or thrombocytopenia, 3) neuromuscular toxicity, or 4) hemodynamic compromise.¹ Patients with no evidence or mild local tissue swelling should not be given antivenom. If the patient meets any of the above criteria, the initial dose of antivenom should be given immediately. The starting dose for treatment is 4-6 vials of administered over one hour. It is important to administer the antivenom slowly, start at 10 mL/h, to reduce the rate of hypersensitivity reactions. This should be repeated until control of patient symptoms has been established, at which time 2 vials every 6 for three additional doses should be administered.¹ To adequately manage a patient and prevent major morbidity or mortality, a minimum of 10 vials should be available.² If the plan of care for a snake bite is to transfer any symptomatic case, a minimum of 4-6 vials should be available to start treatment without delay.

Call your local Poison Control Center for treatment guidance and help identifying local stocks of antivenom. A toxicologist experienced in treating snake bites is always available for further consult. In the above case, the patient did not meet criteria for antivenom administration since there was no noticeable swelling. Additionally, it is important to appreciate that water moccasins are not native to NY, although they have similar features to the Northern Water Snake and the Lake Erie Water Snake. It is always possible that this snake was transferred to the area however, and the decision to use antivenom should be assessed using the above criteria.

References:

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Fomepizole: In Ethylene Glycol Poisoning

Contributed by: Ruth A. Lawrence, MD, Medical Director, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

Case Report:

A 50 year old male is brought to the emergency department having been found inebriated in a parking lot. A large half-empty container of blue anti-freeze was found on the ground. He had vomited, was weakly responsive but speech was unintelligible.

In the ED, his initial labs revealed a large osmolar gap but no acidosis. Over the next hour, he began to hyperventilate and had a seizure. Further laboratory results revealed an osmolar gap 12 mOsm/L, serum bicarbonate of 17 mEq/L, an arterial pH of 7.1 and oxalate crystals in the urine. Eventually, the ethylene glycol level was reported at 150 mg/dL. The patient was stabilized, intubated and ventilated. Intravenous fluids with bicarbonate were started. Seizures were controlled with diazepam.

Treatment of choice is fomepizole or alternatively an ethanol drip could be used to inhibit the generation of toxic metabolites.

The usual patient requires approximately 4 vials in the first 24 hours. The hospital does not have fomepizole and no pharmacist is available to constitute an ethanol drip. They do not do dialysis.

The Poison Center recommends initiation of the fomepizole infusion with loading dose, then transport of patient to tertiary center with either adequate amounts of fomepizole or the capability of preparing an ethanol drip, and the capability of performing urgent dialysis. Since this hospital does not have fomepizole they would need to request emergency delivery of the drug so that adequate protection of the patient can be instituted prior to and during transport.

The advantage of fomepizole compared to ethanol is lack of CNS depression, ease of administration, and ability to reduce the need for dialysis.

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Question from the Drug Information Center

Contributed by: Jamie Nelsen, Pharm.D., Director Drug Information, Upstate NY Poison Center, Syracuse, NY

Question: What is literature for the use of physostigmine in baclofen overdose?

Answer:

Summary

Available literature suggests physostigmine has a very limited role in the reversal of baclofen overdose. A modest benefit has been reported in cases of mild to moderate overdoses, presenting primarily with central nervous system (CNS) depression with or without generally mild respiratory depression. In these instances, physostigmine was noted to increase alertness and consequently improve respiratory drive. In patients administered physostigmine following more consequential baclofen toxicity, physostigmine was of no benefit. In one report, cardiac arrest occurred in a patient receiving physostigmine via continuous infusion. Pharmacologically, there is little rationale for the administration of physostigmine to reverse baclofen toxicity. Additionally, based on the currently available evidence, minimal benefit can be attributed to physostigmine administration and the risk for adverse events including brochorhea, bradycardia, and cardiac arrest, argue against its use for this indication.

Baclofen Pharmacology

Following overdose, clinical toxicity typically includes respiratory depression, muscular hypotonia, and generalized hyporeflexia. Respiratory depression may be more pronounced in instances of intrathecal versus oral overdose. Baclofen is a gamma aminobutyric acid-B (GABA-B) receptor agonist, causing cellular hyperpolarization thought to be responsible for its skeletal muscle relaxant effects.¹ Via its ability to stimulate GABA-B, baclofen has also been shown to inhibit central ace-

tylcholine release thereby reducing the frequency and amplitude of impulse conduction, specifically in the hippocampus.^{2,3} Kommalage et al. evaluated baclofen's effect on intraspinal acetylcholine release similarly reported an inverse relationship between baclofen and acetylcholine concentrations.⁴ The impact of baclofen on intraspinal acetylcholine release may play an important role in the regulation of a patient's pain threshold, but is not known to adversely affect respiratory drive.

Physostigmine

Physostigmine is an acetylcholinesterase inhibitor, thereby blocking the breakdown of acetylcholine in the synapse and increasing available neurotransmitter for binding to target receptors. The role of this drug in the overdose scenario should be limited to the management of anticholinergic toxicity, however its ability to cause CNS stimulation has meant that physostigmine (Antilirium®) has been used inappropriately to treat toxicity for nonanticholinergics.⁵ Central anticholinergic toxicity may range from agitation, delirium, hallucinations, seizures, and coma; it is not characterized by respiratory depression.⁵ The potential benefits of physostigmine need to be weighed against the risks of administration in each scenario. Muscarinic agonism will stimulate respiratory secretions and may compromise airway management. Physostigmine should also be avoided in patients with any evidence of cardiac conduction delays. Atropine should be available at the bedside in the event physostigmine administration results in excessive cholinergic toxicity.⁵

Evidence: Physostigmine & Baclofen

To date, evidence supporting the use of physostigmine for baclofen overdose is minimal and controversial. Muller-Schwe-

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fe et al.⁶ describe three patients who received intrathecal (IT) baclofen at doses of 80, 150, and 800 mcg. All three cases were noted to have drowsiness progressing to profound sedation; two cases reported severe respiratory depression (4-8 breaths per minute). Interestingly, in both of these cases patients were also noted to be vomiting without airway compromise. The third patient's primary problem was sedation. Physostigmine was administered at 1-2 mg via slow IV bolus. The authors noted increased alertness with improvement in respirations in two instances. Based on their experiences, the authors concluded that physostigmine was an effective agent for baclofen overdose.

In contrast to this initial report, Saltuari et al.⁷ reported a patient who inadvertently received 10,000 mcg of baclofen IT, a much higher dose than the previous reported. Despite receiving a total of 14 mg of physostigmine, the patient remained profoundly sedated requiring mechanical ventilation. Similarly, Rushman et al.⁸ found that physostigmine was ineffective at reversing sedation and respiratory depression in a patient who inadvertently received 13,000 mcg of baclofen IT. Delhaas et al.⁹ describe five patients with baclofen overdoses, ranging from 176 mcg to 2400 mcg. Physostigmine was not observed to reverse toxicity in any of the cases following a 10 minute observation period. In most cases physostigmine administration was followed by drainage of cerebral spinal fluid (CSF). In one patient sedation and respiratory depression recurred despite CSF drainage.

A physostigmine infusion was started at 3 mg/h. The patient had a cardiac arrest approximately six hours into the infusion.

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State University of New York



Program Announcements • •

Ruth A. Lawrence: Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

UNY: Our Eleventh Annual Toxicology Teaching Day will be held on November 14, 2007 at the Genesee Grand Hotel in Syracuse. Please mark your calendar!

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

LI: Pre-Registration is required. Please contact Mr. Denis Jao at 516-663-2650 to register. Both Telephone and Televideo broadcasts will be available.

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

Location: New Life Conference Rooms B&C
Winthrop-University Hospital
259 First Street, Mineola, Long Island, New York 11501
Times for ALL Conferences are: 12:15 PM-1:45 PM

Sept 26, 2007

TOPIC: Volatile Substance Abuse Involving 1,1-difluoroethane ("Dust Off").

Speaker: Joseph Avella, MS, FTS-ABFT

Sidney B. Weinburg Center for Forensic Sciences, Suffolk County Health Department, NY

Nov 7, 2007

TOPIC: Update of Common Poisonings and Treatments

Speaker: Michael McGuigan, MD, FACMT, FAAP

Professor of Emergency Medicine, State University of New York at Stony Brook, Medical Consultant Long Island Regional Poison Center at Winthrop University Hospital,

Dec 5, 2007

TOPIC: Food Poisoning

Speaker: Daniel Kuhles, MD, MPH

Clinical Instructor, State University of New York at Stony Brook, Department of Preventive Medicine.

Assistant Director, Division of Disease Control Nassau County Department of Health

Please call administrative telephone numbers for more information.

A "Duster" Inhalational Exposure with Drugs Leads to Death

Contributed by: Henna Rahi, PharmD. Candidate, St. John's University, T Caraccio, PharmD., ABAT, Long Island Regional Poison and Drug Information Center at Winthrop University Hospital, Mineola, NY

Case Report:

A 23-year-old male patient was brought to the emergency department (ED) by emergency medical services after being found on a train platform unresponsive. A witness had observed the patient inhaling a commercial duster product containing a fluorinated hydrocarbon. The patient was pulseless at the scene and upon arrival to the ED.

What is "duster" and what are the inherent toxicities associated with inhaling these products?

A "duster" is a compressed liquid containing single or multiple hydrocarbon containing substances. These hydrocarbons are utilized as a propellant aerosol of gas that is used to remove dust from various surfaces. There are many known hydrocarbon containing household products that are used in various forms as a means of chemical recreation.

Continued on page 4

Toxicology Advice Centers • •

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

Western New York Poison Center (WNY)

716.878.7871 • <http://wnypoison.org>

Ruth A. Lawrence NY Poison Center (FL)

585.273.4155 • www.FingerLakesPoison.org

Upstate New York Poison Center (UNY)

315.464.7078 • www.upstatepoison.org

New York City Poison Control Center (NYC)

212.447.8152

Long Island Poison & Drug Info Center (LI)

516.663.4574 • www.LIRPDIC.org

Toothpaste Imported From China May Contain Diethylene Glycol

6/13/2007 Gold City Enterprise LLC of Hallandale, Florida initiated a nationwide recall of toothpaste made in China because the products may contain the poisonous chemical diethylene glycol (DEG), a substance used in antifreeze and as a solvent.

Unapproved Guaifenesin Timed-Release Drug Products

05/25/2007 FDA informed consumers and healthcare professionals of its intent to take action against companies that market unapproved timed-release dosage form of guaifenesin products, a substance commonly used in medicines to relieve cough and cold symptoms by stimulating removal of mucous from the lungs.

Exjade (deferasirox) Tablets For Oral Suspension

05/22/2007 Novartis and FDA notified healthcare professionals of changes to the WARNINGS and ADVERSE REACTIONS sections of the product labeling for Exjade, a drug used to treat chronic iron overload due to blood transfusions (transfusional hemosiderosis) in patients 2 years of age and older. Cases of acute renal failure, some with a fatal outcome, have been reported following the post marketing use of Exjade.

Avandia (rosiglitazone)

05/21/2007 FDA informed healthcare professionals of a potential safety issue related to Avandia (rosiglitazone). An on-going analysis of safety data for the treatment of type 2 diabetes mellitus using Avandia showed differing rates of ischemic cardiovascular events including heart attack or heart-related adverse events, some fatal, relative to other drugs used to treat diabetes mellitus.

Caffeine Citrated, Powder, Purified

05/21/2007 Spectrum and FDA informed healthcare professionals of a nationwide recall of 3 lots (TS0225, UK0821, and V11203) of Caffeine Citrated, Powder, Purified. The product was recalled because of complaints about potential sub potency.

NBTY Shark Cartilage Capsules

06/06/07 Action Labs recalled its Sentinel brand of Shark Cartilage capsules manufactured by NBTY in 2005 because the product may be contaminated with Salmonella.

OxyContin, Illegal Promotion by Manufacturer May Cause Health Risks for Consumers

05/10/2007 FDA informed healthcare professionals of criminal charges and civil liabilities brought against Purdue Frederick in connection with several illegal schemes to promote, market and sell OxyContin, a powerful prescription pain reliever that the company produces.

True Man and Energy Max Products

05/10/2007 FDA informed consumers and healthcare professionals regarding the dangers associated with the pur-

chase or use of True Man or Energy Max products promoted and sold as dietary supplements throughout the United States. Both products, promoted as sexual enhancement products and as treatment for erectile dysfunction (ED), are illegal drug products that contain potentially harmful, undeclared ingredients.

Glycerin compounded products

05/07/2007 FDA warned pharmaceutical manufacturers, suppliers, drug repackers, and healthcare professionals who compound medications using glycerin of the importance of assuring that the glycerin used is not contaminated with diethylene glycol (DEG), a known poison used in antifreeze and as a solvent.

Antidepressant Medication Products

05/02/2007 FDA notified healthcare professionals that the Agency proposed that makers of all antidepressant medications update the existing black box warning on the prescribing information for their products to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

Colchicine Compounded Injectable Products

05/02/2007 ApothéCure and FDA notified all healthcare professionals of recent deaths associated with the use of compounded injectable Colchicine 0.5mg/ml, 4ml vials, lot number 20070122@26.

Warning About Counterfeit Drugs From Multiple Internet Sellers

05/01/2007 FDA informed consumers and healthcare professionals regarding the dangers associated with buying prescription drugs over the internet. FDA received information showing that 24 apparently related websites may be involved in the distribution of counterfeit prescription drugs.

PharmaFab Inc., manufacturer and distributor of prescription and over-the-counter drug products

04/25/2007 FDA announced the entry of a Consent Decree of Permanent Injunction against PharmaFab Inc., its subsidiary, Pfab LP, and two company officials, to stop the illegal manufacture and distribution of prescription and over-the-counter drug products.

Avastin (bevacizumab)

04/21/2007 Genentech and FDA notified healthcare professionals of important new safety information regarding tracheoesophageal (TE) fistula formation in a recent clinical study in patients with limited-stage small cell lung cancer (SCLC).

Zanaflex (tizanidine hydrochloride) Tablets and Capsules

04/11/2007 Acorda Therapeutics and FDA informed healthcare professionals of changes to the CONTRAINDICA-

Continued on page 3

FDA Safety Summaries

Continued from page 2

TIONS and WARNINGS Sections of the product labeling for Zanaflex, a drug used to treat spasticity. In pharmacokinetic studies where tizanidine was coadministered with either fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects.

Ziagen (abacavir sulfate) Tablets Combivir (lamivudine and zidovudine) Tablets

04/10/2007 GlaxoSmithKline and FDA informed health-care professionals of an apparent third-party tampering that resulted in the misbranding of Ziagen as Combivir and employed counterfeit labels for Combivir Tablets.

Grifulvin V (griseofulvin) Oral Suspension Griseofulvin Oral Suspension

04/10/2007 Ortho-McNeil and FDA informed health-care professionals and consumers of a nationwide recall of griseofulvin oral suspension, a prescription medication used to treat ringworm and other fungal infections. The recall was issued based on two reports of glass fragments found in bottles of the liquid formulation.

Trimethobenzamide hydrochloride Suppositories

04/06/2007 FDA notified healthcare professionals and consumers that companies must stop manufacturing and distributing unapproved suppository drug products containing trimethobenzamide hydrochloride.

Zelnorm (tegaserod maleate)

03/30/2007 FDA notified healthcare professionals and patients that Novartis has agreed to discontinue marketing Zelnorm, a drug used for the short-term treatment of women with irritable bowel syndrome with constipation and for patients younger than 65 years of age with chronic constipation. FDA analysis of safety data pooled from 29 clinical trials involving over 18,000 patients showed an excess number of serious cardiovascular adverse events, including angina, heart attacks, and stroke, in patients taking Zelnorm compared to patients given placebo.

Permax (pergolide) and generic equivalents

Posted 03/29/2007 FDA notified healthcare professionals and patients that companies that manufacture and distribute pergolide have agreed to withdraw the drug from the market. Pergolide is a dopamine agonist (DA) used with levodopa and carbidopa to manage the signs and symptoms of Parkinson's disease. Results of two new studies showed that some patients with Parkinson's disease treated with pergolide had serious damage to their heart valves when compared to patients who did not receive the drug.

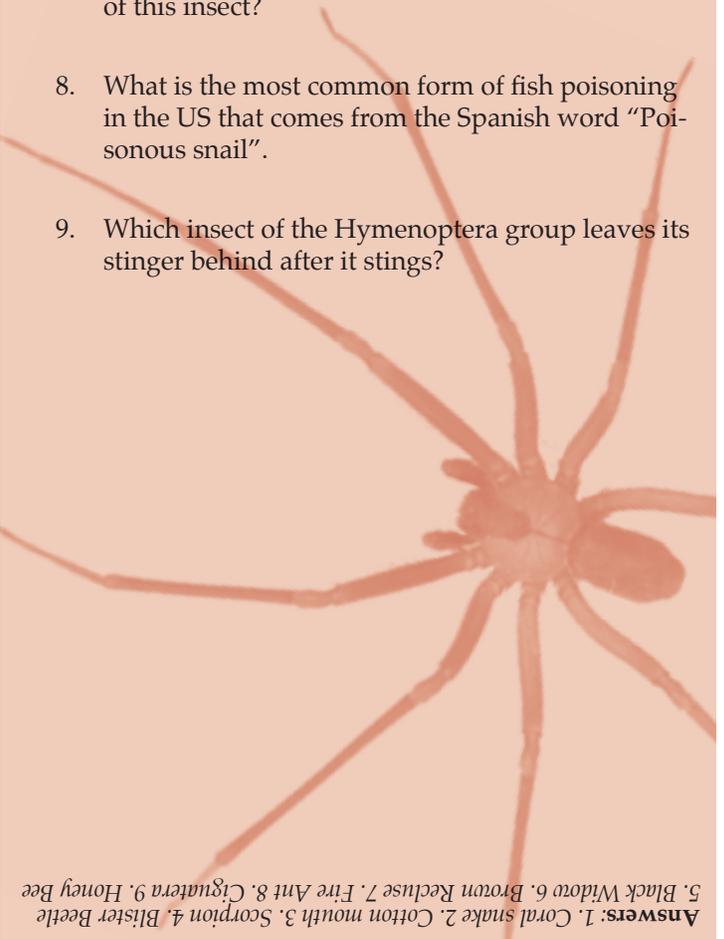
Accutane (isotretinoin)

Posted 03/28/2007 FDA notified consumers and healthcare professionals of a special webpage launched to warn about the dangers of buying isotretinoin online.

Tox Trivia ••

Insect/animal questions

1. What is the common name of the snake in North America which is toxicologically related to the Cobra?
2. What is the common name of the snake *Agkistrodon piscivorus leucostoma* that is a member of the pit viper family?
3. Which venomous animal was able to withstand the most radiation when exposed to nuclear weapons in the Sahara desert when tested by the French?
4. Which insect is Spanish Fly produced from?
5. What is the common name of the poisonous spider called *Latrodectus mactan*?
6. What is the common name of the poisonous spider called *Loxosceles*?
7. The insect of the genus *Solenopsis* can produce a vicious bite and sting. What is the common name of this insect?
8. What is the most common form of fish poisoning in the US that comes from the Spanish word "Poisonous snail".
9. Which insect of the Hymenoptera group leaves its stinger behind after it stings?



Answers: 1. Coral snake 2. Cotton mouth 3. Scorpion 4. Blister Beetle 5. Black Widow 6. Brown Recluse 7. Fire Ant 8. Ciguatera 9. Honey Bee

Some common names and associated chemical substances of those used for inhalation are listed in Table 1.

Table 1 – Examples of Commonly Abused Inhalational Hydrocarbons

Common name	Hydrocarbon
Airplane glue	Toluene
Cigarette Lighter	Butane
Duster	Difluoroethane
Spot remover	Tetrachloroethylene
Typewriter correction	Trichloroethane

Hydrocarbons, by nature are composed of carbon and hydrogen atoms generally found in either an aliphatic (straight) or aromatic (cyclic) arrangement. Expected signs of use and toxicity of the various hydrocarbons relates to several physicochemical factors, including the number of carbons in the compound, the number and types of branches, and/ or the functional groups attached to the hydrocarbon chain/ring, as well as to the route of exposure.

Acute inhalation exposure

Common to inhalational recreational use of hydrocarbons is central nervous system depression caused by enhanced inhibitory tone as well as from decreased fractional inspired oxygen during use. The method of inhalational use can be described using the terms “sniffing”, “huffing” or “bagging”. Sniffing implies nasal or oral infiltration directly from the source substance. Huffing requires pouring a liquid form of the hydrocarbon onto a cloth or like substance and holding near the mouth or nose to inspire. Finally, bagging, which leads to the most profound decreased in inspired oxygen, is when the hydrocarbon is placed in a bag and then inspired directly. Central nervous system depression is generally not life threatening, although concomitant respiratory depression may occur.

After acute use, the most consequential toxicity noted with some aromatic and in particular halogenated hydrocarbons is cardiac dysrhythmias. The mechanism appears to be related to a prolongation of ventricular repolarization manifested by a prolonged corrected QT interval. (See Figure 1) Prolongation of repolarization leads to a longer relative refractory period, which is then available for capture by early afterdepolarizations. Stimulation of the beta-1 adrenergic receptor, either endogenous or exogenous can provide a stimulus for these afterdepolarizations.

Chronic use

Most organ systems can be affected by chronic inhalational hydrocarbon use. Organ system involvement may be specific to the hydrocarbon used. For example, chronic use of chloroform and tetrachloroethylene results in hepatotoxicity, while n-hexane results in peripheral neuropathy and toluene results in renal tubular acidosis.

Other

Rarely, acute use can result in pulmonary toxicity if the hydrocarbon in inadvertently aspirated. Pulmonary aspiration inactivated the surfactant necessary to maintain the integrity of the alveoli. Secondary inflammation may result in impaired oxygenation and decreased lung compliance as seen in the respiratory distress syndrome. Here central nervous system depression is more prolonged and a manifestation of hypoxemia. Skin contact may result in defatting dermatitis, due to dissolution of dermal oils.

What initial management should be provided for a patient with an inhalational hydrocarbon exposure?

- 1) ABC's: Airway breathing and circulation. Remove the patient from the exposure into a fresh air environment. Patients should be provided 100% oxygenation and intravenous fluids at a minimum, but care is no different that other patients arriving to the emergency department.
- 2) Disability: Altered mental status. The patient should be assessed rapidly for hypoglycemia.
- 3) Supportive Care:
 - a. Stable patients should receive a careful history and physical examination. Symptoms of altered mental status should decline over time.
 - b. Unstable patients should receive resuscitation efforts. An exception is that patients exhibiting dysrhythmia or prolonged Qtc duration may benefit from the addition of a beta adrenergic antagonist. As these agents reduce cardiac ionotropy which may further compromise cardiac output, using a short-acting agent such as esmolol may be preferable.
 - c. Patients presenting with signs of hydrocarbon aspiration should receive aggressive supportive pulmonary care including use of high positive end expiratory pressure therapy when required.
- 4) Laboratory Studies:
 - a. ECG – for dysrhythmias and to measure QTc interval duration
 - b. BMP, LFTs – alterations in acid/base balance, renal or hepatic function
 - c. CT/MRI brain – for persistent neurologic findings.

Why may beta adrenergic antagonists be beneficial for Qtc prolongation?

Prolongation of cardiac repolarization when seen after inhalational hydrocarbon abuse is caused by inhibition of the rapid component of the delayed rectifier potassium current (Ikr). Functionally, this drug/toxin related change

is similar to congenital causes of delayed repolarization in that there is a delayed time in each action potential in which an early after-depolarization (stimulus for another action potential during the relatively refractory period) can occur. When this occurs a consequence may be the development of a non-perfusing cardiac dysrhythmia, torsades de pointes. Inhibition of the beta-1 adrenergic receptor activity may provide benefit by decreasing the potential for a stimulus to occur during the relatively refractory period by blunting endogenous adrenalin or exogenous sources of norepinephrine or epinephrine activity.

Are there any therapeutic measures for signs of other end organ acute or chronic toxicity?

Hepatotoxicity – Patients presenting with hydrocarbon related hepatotoxicity should be treated using N-acetylcysteine as some animal models and human case series indicate that it may mitigate toxicity.

Nephrotoxicity – (e.g., renal tubular acidosis with hypokalemia after toluene abuse) These patients should be treated supportively with careful supplementation of potassium as needed.

Neurotoxicity – Peripheral neurotoxicity is typically manifested as an axonopathy, which should be treated supportively and may resolve over time. Leukoencephalopathy, due to destruction of the central nervous system white matter, has no known therapy and is not known to be reversible.

What is the Data with Duster containing Difluoroethane toxicity?

There are four cases resulting in mortality associated with possible difluoroethane exposure. In two of the cases, the patients died in motor vehicle accidents. In the first case, a surviving passenger stated that the patient was inhaling a difluoroethane duster prior to losing control of the car. In the second, two passengers of a car died when their vehicle crossed over the median of a four lane highway; their blood levels showed difluoroethane and the can of the aerosolized airbrush propellant was found in vehicle. In a third case, a man was found dead on the floor next to his computer with an empty can and another nearly full can of a difluoroethane duster. Inhalation of the difluoroethane was the cause of death. The fourth case involved a man found dead after repeated exposure to difluoroethane. The cause of death was determined to be fatal arrhythmia due to intoxication with difluoroethane.

The table at the top of the next column illustrates tissue concentrations of difluoroethane in two of fatal cases of difluoroethane exposure published in the literature:

TISSUE	POST-MORTEM DIFLUORETHANE CONCENTRATION	
	<i>Xiong Et Al</i>	<i>Avella J Et Al</i>
Femoral Blood	83.5 mg/L	136.3 mg/L
Brain	43.8 mg/kg	117.5 mg/kg
Lung	91.1 mg/kg	60.3 mg/kg
Liver	92.7 mg/kg	87.6 mg/kg
Kidney	24.3 mg/kg	-
Muscle	80.5 mg/kg	-
Adipose	29.8 mg/kg	235.7 mg/kg
Pulmonary Blood	141.1 mg/L	-
Aortic Blood	122.7 mg/L	-
Vitreous	-	25.1 mg/L

Laboratory and Hospital Course

Initial management consisted of intubation, successful resuscitation and stabilization with supportive care. The patient remained unresponsive and was transferred to the cardiac care unit. In the CCU, the patient displayed intermittent spontaneous respirations while on the ventilator but continued to be unresponsive despite titration of sedation.

	Level	Range
Sodium	142	138-145 mEq/L
Potassium	3.6*	3.7-5.2 mEq/L
Chloride	106	103-112 mEq/L
CO ₂	19.8*	22-33 mEq/L
Glucose	268*	73-107 mEq/L
BUN	18	5-21 mg/dl
Creatinine	1.7*	0.4-1.2 mg/dl
Anion Gap	16.2	8-12 mg/dl
PT	12.0	10-13.8 sec
PTT	<20*	21.9-42 sec
INR	0.99	0.7-1.2
Bilirubin	0.14*	0.3-1.1 mg/dl
AST	30	0-41 IU/L
ALT	37	0-45 IU/L
Calcium	9.0	8.6-10 mg/dl

*= out of normal range

His troponin-I level was not detectible. [put troponin in table?] An arterial blood gas performed ten hours after presentation revealed: pH, 7.245; pCO₂, 50.4; pO₂, 568; HCO₃, 21.1; O₂ saturation 100%. The toxicology laboratory results were negative for acetaminophen, salicylates and ethanol. A rapid toxicology screen was positive for opiates and PCP, but negative for other drugs of abuse.

SPI CORNER: PRODUCT RECALLS

Contributed by: T. Michele Caliva, RN CSPI, Upstate New York Poison Center, Syracuse, NY

In this fast paced information age consumers receive product recall information at an amazing rate. In fact, they may often receive information before those of us in health care settings are made aware of it. While much of this information is useful, some - particularly reports regarding product recalls - can be unduly alarming.

What is the role of the Poison Center when a product is recalled and how can a Poison Center support local emergency departments and health practitioners through the inevitable influx of callers and patient visits?

Poison Centers can assist health care providers in a variety of ways such as handling questions from the general public, providing health care providers with the most current treatment guidelines, collecting data for departments of health, and managing media inquiries.

During the recent peanut butter scare, Poison Centers not only provided information on lot numbers and symptoms of salmonella poisoning, but they also provided reassurance to callers who were asymptomatic although frightened that they might be affected.

During last summer's spinach e-coli recall Poison Centers played a critical role by collecting information on the number of calls, the areas from which the calls were originating, and by tracking callers' symptoms and outcomes.

It is not unusual for a Poison Center to receive calls from the media during a recall - such as the current concern over toothpaste contaminated with diethylene glycol. The Poison Center staff is often able to use these opportunities to quell fears and dispel myths. These interviews provide a forum for the dissemination of correct information on the seriousness of the recall and hopefully prevent unnecessary emergency department visits.

Poison Centers can also support health care providers during recalls by providing front line staff with the most current recall information, updates on anticipated symptoms, management recommendations, observation guidelines and discharge instructions.

In the case of a serious situation such a botulism exposure, the Poison Center staff will work with the DOH and the CDC in obtaining botulinum antitoxin. In any exposure that requires an antidote the Poison Center staff can facilitate the prompt transfer of an antidote from one facility to another.

Reaching out to the public during a crisis such as a recall is vital. Reducing the panic and providing the general public with clear directions and guidance is essential. Health Care Providers can rely on the ready infrastructure and experience of Poison Center's staff in managing public inquiries and exposures. This should help reduce the stress and workload of health care providers, minimize unnecessary ED visits and help to facilitate the prompt treatment of patients if indicated.

A "Duster" Inhalational Exposure...

Continued from page 5

The patient developed a pneumonia, presumably secondary to aspiration, which was treated with antibiotics. The patient's cardiac enzymes became elevated on the second day of admission with a peak CPK of 1464 and a troponin level of 2.96. Over the next few weeks, the patient's condition did not improve, and he never regained consciousness. The family decided to issue a DNR order and the patient was extubated and terminally weaned. Over the next few days, the patient's condition rapidly deteriorated and he expired on the 20th day post admission from a cardiopulmonary arrest.

Select References

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- Williams DR. Cole SJ. Ventricular fibrillation following butane gas inhalation. *Resuscitation.* 1998; 37(1):43-5.



Contributed by: Jamie Nelsen, Pharm.D., Director Drug Information, Upstate NY Poison Center, Syracuse, NY

Question: What is the mechanism for N-acetylcysteine elevating INR? Is this elevation consequential?

Answer:

Background

N-acetylcysteine (NAC) is used to prevent acetaminophen-induced hepatotoxicity. One marker of acute liver injury is hemostatic dysfunction (elevated PT) resulting from an inability to synthesize clotting factors. NAC has been associated with decreased activity of several vitamin K dependent clotting factors both in vitro and in healthy human volunteers.(1) In patients being evaluated for acute liver dysfunction secondary to acetaminophen (APAP) toxicity, changes in clotting activity secondary to NAC administration may result in an unreliable estimation of real hepatic injury.

NAC & Anticoagulation

Knudsen et al.(1) prospectively evaluated the prothrombin time in ten healthy volunteers following the IV administration of NAC. Serial blood draws were performed at 0, 3, 6, 8, 12, 16, 24, 32, 38, 48, 72, and 120 hours. The activities of factors II, VII, IX, and X decreased significantly within one hour of administration of NAC. In all instances this was followed by an increase in factor activity. Factor II and IX activities returned to baseline by six hours following infusion while factor VII activity returned to baseline at 38 hours. Factor X activity was sustained at ~70-80% of baseline values until normalizing at 72-120 hours.

Several case reports have described prolongation of the prothrombin time in patients being treated with intravenous NAC without other evidence of hepatotoxicity.(2,3,4,5) Lucena et al.(4) retrospectively evaluated 18 patients who received IV NAC for APAP toxicity. All patients had an AST and ALT concentrations of <30 U/l and < 40 U/l, respectively. After initiation of NAC, the prothrombin time increased by 21% (range, 4.8-53.4%) relative to baseline ($p < 0.0001$). This decrease was evident within a median time of 14h (range 2-46 h). By the end of NAC therapy, all prothrombin times had approached baseline values. These findings are consistent with other reports. Schmidt et al.(3) retrospectively evaluated the records of 87 patients admitted for APAP toxicity and having received IV NAC. At 7.7 h after initiation of IV NAC therapy, prothrombin time had increased by 33% (0.29-0.38%). This effect, similar to the aforementioned report, was more pronounced with the start of therapy and diminished with time.

The basis for this adverse effect is not well defined although two mechanisms have been proposed. Vitamin K

dependent proteins are homologous multi-domain proteins that share a unique 'Gla' domain. It is proposed that NAC affects the structure/ function of these proteins either via denitrosylation of the protein or reduction of the exposed disulphide bonds.(1) The effect appears to be dose dependent and would account for the relative restoration in clotting activity following administration of the initial bolus recommended in patients receiving NAC secondary to APAP poisoning.

The bioavailability of NAC following oral administration is approximately 10-30%.(6) It is unknown to what degree, if any, the prothrombin time may be increased following oral NAC therapy.

Summary

In conclusion, it appears that NAC prolongs the prothrombin time following IV administration. This affect is dose related and is most pronounced following the initial bolus recommended to treat APAP poisoned patients. An initial increase in prothrombin time of up to ~33% of baseline value may be expected. Although there is significant interpatient variation, NAC's effect on the prothrombin time is diminished with ongoing therapy and in most instances has normalized by the end of therapy.

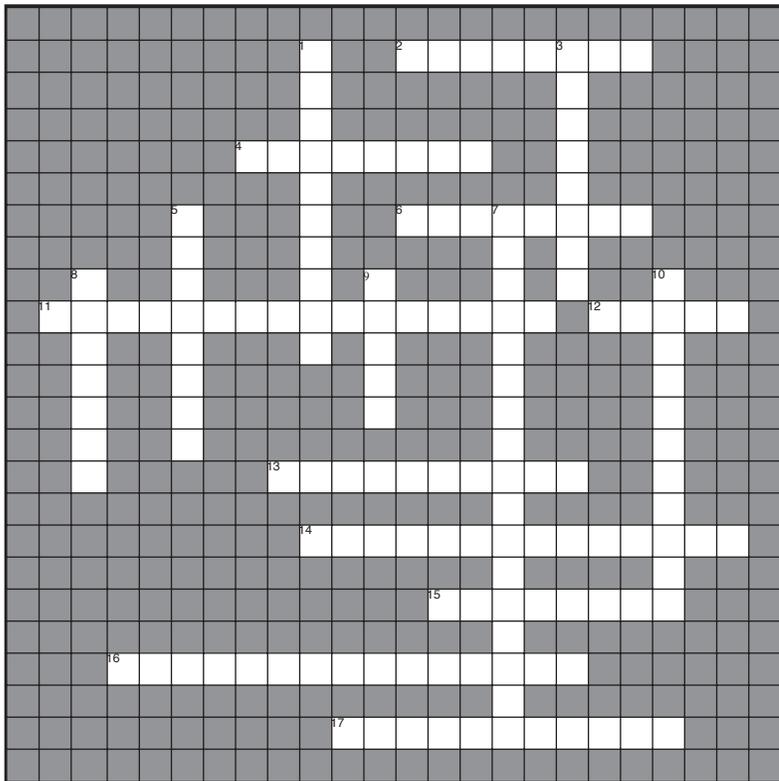
When evaluating a patient for acetaminophen-induced liver failure, it is extremely important to consider other parameters besides the prothrombin time. Poor prognostic markers in patients with APAP-induced liver failure include:(6) pH < 7.3 after fluid and hemodynamic resuscitation OR the combination of PT > 100s, creatinine > 3.3 mg/dL, and grade III/IV encephalopathy. In addition a serum phosphate concentration > 3.75 mg/dL 48-72h following exposure and an APACHE score > 15 in isolated APAP ingestions may also be indicative of poor outcome without transplantation.(6) Since NAC is only expected to mildly elevate the PT (~1/3 of baseline), this adverse effect should not be consequential in the overall assessment of the APAP poisoned patient.

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TOXICOLOGY CROSSWORD

POISON GASES



ANSWERS: 1. Salivation 2. Smallpox 3. Phosgene 4. Avian Flu 5. Chlorine 6. Phosgene 7. Sodium Thiocyanate 8. Cyanide 9. Sarin 10. Pralidoxime 11. Hydroxycobalamin 12. Kurds 13. Descending 14. Pyridostigmine 15. Chlorine 16. Dimethylsulfate 17. Hematemesis

ACROSS

2. Potential biowarfare agent causing a cluster of similarly appearing pustule lesions with rapidly rising fever
4. Common name of H5N1 is a sub type virus
6. Smells like freshly cut grass
11. Chemical name new cyanide antidote
12. Ethnic group who suffered the effects of a poisonous gas used by Saddam Hussein's forces
13. Direction of Botox® related paralysis
14. Bromide Drug given to US troops in the Persian Gulf War to mitigate nerve gas exposure
15. Cannon shells were filled with this during the American Civil War
16. Chemical name of "D Stoff" or "Rationite" was used as a war gas
17. 3 "H" critical gastrointestinal effects of pneumonic plague include: Hemorrhagic diarrhea, Hemoptysis and ___.

DOWN

1. Oral cholinergic caused by organophosphate nerve agent SARIN
3. Poison gas used against the Allies in WWII
5. Irritant gas can causing non cardiogenic pulmonary edema
7. Antidote traditionally used for cyanide poisoning
8. Chemical used in suicides during the closing days of WWII
9. Name of the poison gas that Saddam Hussein's army used in the 1980's
10. Nerve Agent Antidote Kit (NAAK) contains atropine and ___.

