



Central
New York
Regional
Poison
Control
Center

The CNYPC

January 1997

Toxicology Letter

Vol. II No. 1

A Quarterly Publication

SCHEDULED EVENTS:

S.U.N.Y., H.S.C. Department of
Emergency Medicine

Emergency Medicine Grand Rounds

Marley Education Center; Sulzle Auditorium
Third Friday of the Month, 11:00 AM

Jan. 17 Plant Toxicology

Feb. 21 Emergent Problems of Renal
Transplant Patients

March 21 Gastrointestinal Emergencies

Toxicology Case Conference

CNYPC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 11:00 AM - 12:00 PM

HISTORICAL TID BITS:

1. According to the 1995 report of the AAPCC TESS, these agents have surpassed antidepressants and stimulants in terms of percent death per exposure?
2. What year was the first poison control center started?
3. What was the major health effect from the use of "agent orange"?

TOX TRIVIA:

1. What fruit (that can be purchased at Wegmans) can cause hypoglycemia?
2. What toxin can cause thiamine deficiency, especially in animals?
3. What is the most common adverse effect from ingesting the poinsettia plant?

CLINICAL TOXICOLOGY PEARLS:

Systemic hypocalcemia may occur after hydrofluoric acid dermal burns to as little as 2.5% of the BSA.

Hypoglycemia can rarely present with focal neurologic findings on physical examination.

Oral hypoglycemics may produce delayed toxicity in children that does not correlate with the drugs pharmacokinetics.

Introduction

The CNYPC toxicology letter has recently expanded in the following areas: a) our case section will now be three pages, b) there will be a crossword puzzle area, c) there will be a poison information specialists contributed area. We will continue to list our scheduled events, detail historical tidbits, tox trivia, and clinical toxicology pearls. We hope you enjoy receiving the CNYPC toxicology letter and invite you to comment or join our mailing list at any time by contacting the CNYPC at 315-476-4766.

CASE HISTORY

Contributed by: Christine M. Stork, Pharm.D., ABAT

CARDIAC POISONS

A 16 year old female is brought into the emergency department approximately 2 hours after an intentional exposure to numerous medications. Reported medications included unknown amounts of verapamil 240 mg sustained-release tablets, bisoprolol 2.5 mg/hydrochlorothiazide tablets, hydroxyzine tablets and a cough and cold elixir. She is lethargic, but responds to loud verbal stimuli. Her pupils are 3 mm, equal round and reactive. Her heart rate is 60 bpm, blood pressure is 50/p mmHg, respiratory rate is 14 bpm and temperature is 36.9 C. Physical examination reveals decreased bowel activity, and moist mucous membranes, and otherwise is non-contributory. The patient has received 2 L of normal saline without response and the heart rate now falls to 30 and is considered a junctional rhythm on ECG.

What are the immediate concerns to address in this patient?

This patient has been exposed to a potentially lethal dose of a calcium channel antagonist (CCB) or a beta adrenergic antagonist (BB). The patient does not appear to be anticholinergic (history of hydroxyzine exposure) due to the presence of moist mucous membranes, lack of tachycardia and pinpoint pupils. As with any other life-threatening exposure, careful attention to the ABC's (airway, breathing and circulation) should take precedence. The patient's airway is patent and the patient is breathing. Circulation may require some pharmacological intervention specific to CCB or BB poisoning. In addition, this patient has an altered mental status. An accurate blood glucose determination or glucose 1 g/kg should be administered and thiamine 100 mg should be considered for those who are alcoholic or otherwise malnourished.

What are the expected laboratory abnormalities in CCB/BB poisoning?

Calcium channel antagonists may produce hyperglycemia through a calcium channel mediated mechanism at the beta islet cells of the pancreas. Calcium channel agonists in the pancreas (along with beta adrenergic agonists) stimulate insulin release. In fact, CCB are being studied for their possible role in the treatment of insulinomas. Changes in calcium homeostasis after CCB overdose, however, are not typically seen. Beta adrenergic antagonists can cause hypoglycemia and hyperkalemia or exacerbate underlying hypoglycemia through a beta mediated effect.

What is the Differential for toxin associated bradycardia/hypotension?

Other toxins that commonly cause bradycardia include; digoxin, organophosphates, central alpha adrenergic agonists (i.e. clonidine), electrolyte abnormalities, antidysrhythmics, and peripheral alpha adrenergic agonists (i.e. phenylpropanolamine). Sedative hypnotics and opioids also can cause small decreases

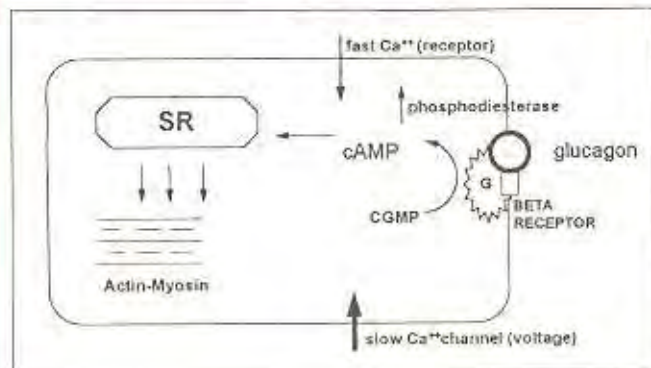
Continued on page 2

Answers on page 3

CARDIAC POISONS -continued

in pulse. Hypotension may be caused by digoxin, clonidine, alpha 2 adrenergic antagonists (i.e. phenothiazines, phentolamine/prazosin), direct vasodilators (i.e. nitroprusside), angiotensin converting enzyme inhibitors, angiotensin-2 antagonists, ganglionic blockers (i.e. reserpine), beta agonists (i.e. albuterol) and others that decrease perceived intravascular volume. In addition, sedative hypnotics and opioids can cause small decreases in blood pressure.

What are the specific therapies for CCB/BB poisoning that result in hypotension/bradycardia?



CCB inhibit calcium influx through slow voltage sensitive (L) calcium channels. This, in turn, inhibits activation of fast calcium channels and release of calcium from the SR (sarcoplasmic reticulum) to cause actin and myosin complexation. In addition, in high doses, CCB may antagonize alpha adrenergic receptors peripherally resulting in additive hypotension. Arteriolar vascular beds, the AV node and the SA node are dependent on the activity of slow calcium channel for the formation of action potentials which leads to vasodilation, decreased automaticity and bradycardia.

The beta adrenergic receptor acts through a G protein to increase the conversion of cGMP to cAMP. cAMP is a second messenger which increases contractility by increasing the release of calcium from the SR. cAMP is degraded through the activity of the enzyme phosphodiesterase. BB inhibit the production of cAMP. Therapy for both CCB and BB poisoning is aimed at increasing intracellular calcium by increasing intracellular cAMP or by an increase in the direct supply of calcium.

• FLUID

Fluids (crystalloid) increase intravascular volume by expanding the extravascular space. They are considered first line therapy for toxin associated hypotension of all causes. They may be less useful in the setting of CCB/BB poisoning because of concurrent myocardial depression.

• ATROPINE

Atropine inhibits the activity of the vagal nerve. It is considered first line therapy for all causes of toxin associated bradycardia. However, in the setting of CCB/BB poisoning, there have been many reported cases of treatment failure.

• CALCIUM

Calcium competes for slow calcium channel transport and is beneficial in both CCB and BB poisoning. In adults with good peripheral venous access, 3 grams of calcium chloride may be given intravenously (IV) in an otherwise healthy patient at a maximum rate of 1 mL/minute. Each gram of calcium chloride provides 13.6 mEq of calcium. Calcium gluconate may also be used but requires approximately three times the dose to achieve a similar dose of calcium (1 gram = 4.5 mEq calcium). Excessive dosing of calcium may lead to systemic hypercalcemia. To avoid hypercalcemia, serum calcium should be monitored if more than

3 g of calcium chloride (9 g of calcium gluconate) is administered.

• GLUCAGON

Glucagon increases the production of cAMP through a non-beta receptor mediated mechanism. Glucagon is useful for both CCB and BB poisoning, but may be more useful in the setting of BB overdose (use before calcium). The adult dose is up to 10 mg slow IV in divided doses. An additional 2-5 mg/hr IV is also required as maintenance. The package diluent for glucagon contains phenol which may be toxic with excessive dosing and should be substituted with D5W for continuous infusions. Blood glucose concentrations should be closely monitored.

• PACING/VASOPRESSORS/MYOCARDIAL STIMULANTS

Patients not responding to calcium and glucagon require aggressive supportive care. Pacing (external and internal) may be attempted at this point, although there have been several cases of failure of pacing in the setting of BB/CCB overdose. Drugs aimed at maintaining perfusion may include dopamine, norepinephrine, epinephrine, dobutamine, and isoproterenol. Since these patients are hypotensive and bradycardia, it makes sense to initiate therapy with an agent with a pharmacological mechanism that increases beta-1 (myocardial stimulant) and alpha-1 (peripheral vasoconstricting) activity (i.e. norepinephrine). However, to optimize support, invasive hemodynamic monitoring may be warranted.

• AMRINONE

Amrinone inhibits the breakdown of cAMP by acting as a phosphodiesterase inhibitor. There have been cases of patients responding to amrinone/vasopressor combinations that have not responded to vasopressors alone. Patients in which amrinone is considered should have hemodynamic monitoring in place and vasopressors on board since amrinone may induce hypotension.

• INTRAORTIC BALLOON PUMP / CARDIOPULMONARY BYPASS

Both procedures have been used successfully when other modalities have failed in the treatment of CCB/BB overdose. It is wise to evaluate your own institution's capabilities to achieve these procedures early in the course of therapy.

Are there any special concerns with calcium administration or cardiac pacing in a patient with toxin associated bradycardia?

The concerns associated with calcium administration and cardiac pacing stem from the possibility that the patient may be digoxin poisoned. In animals, the administration of calcium worsens the cardiotoxicity associated with digoxin and may produce death. Also, digoxin increases ventricular irritability and at least with internal pacing, has been associated with an increase in ventricular dysrhythmias. In a patient in which there is known or suspected digoxin toxicity, calcium should not be administered as part of the patient's therapy and pacing should be avoided, if at all possible. In those patients with concurrent digoxin and CCB/BB poisoning, the patient should receive treatment for digoxin poisoning (digoxin Fab fragments) before calcium and pacing is considered.

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

None of the available therapies for CCB/BB poisoning are universally effective in the management of poisoning. Significant morbidity and mortality are still associated with these toxins despite recent advances in their critical management. According to the American Association of Poison Control Center's Toxic Exposure Surveillance System in 1995, there were 82 deaths attributed to CCB/BB poisoning (total treated in health care facility is 8407). Therefore, there has been great interest in the development of new agents that may be more beneficial in CCB/BB poisoning management.

Some agents that are in the research stage for the treatment of CCB/BB poisoning include 4-aminopyridine and insulin/glucose administration. 4-aminopyridine (4-AP) inhibits potassium efflux from presynaptic terminals and is currently used as an orphan

Continued on next page

CARDIAC POISONS -continued

drug in the treatment of multiple sclerosis. Potential problems with the administration of 4-AP include seizure activity which has been noted in the MS patients. Insulin and glucose have been studied in an attempt to increase intracellular potassium with some success in the animal model.

What is the typical course of CCB/BB Poisoning?

Regular released BB/CCB poisoning usually becomes apparent within 1-2 hours after oral dosing and almost immediately after intravenous dosing. Sustained released CCB/BB often have a delayed presentation of up to 12 to 24 hours. The typical manifestations of toxicity include hypotension and bradycardia. Sinus bradycardia may progress to various degrees of heart block in severely poisoned patients. Those patients that do not respond to therapy may go on to develop cardiovascular collapse. However, even severely poisoned patients that survive usually maintain neurologic function. In fact, mental status is usually preserved until very late in the course of toxicity. Otherwise the physical examination may reveal decreased bowel activity with CCB.

Is there anything special with regard to gastrointestinal decontamination with sustained release products?

Sustained release products may be too large to fit up an orogastric tube. Syrup of ipecac may be attempted in patients with long patient transport times to an Emergency Department in which the particular agent is not likely to cause acute central nervous system depression. CCB/BB adhere well to activated charcoal, however, large gastrointestinal tract (GIT) burdens may limit the usefulness of activated charcoal alone (i.e. #100, 240 mg verapamil SR tablets would require 240 grams of activated charcoal to achieve a 10:1 charcoal to drug ratio). Whole bowel irrigation has recently been advocated in the treatment of those patients with large GIT burdens in which there is adequate bowel activity. In these cases, a polyethylene glycol electrolyte neutral solution (i.e. GoLightly, NuLightly) is given at 2 L/hr orally until the rectal effluent is clear (up to 25 mL/kg/hr in children). The process takes approximately 4-6 hrs to complete and may prevent toxicity in patients that would not otherwise manifest signs or symptoms of toxicity for 12-24 hours.

Are all the BB alike?

The beta adrenergic antagonists all act as antagonists at the beta adrenergic receptor. Some have "selectivity" at the beta 1 adrenergic receptor, however, receptor selectivity is lost in the overdose setting. Also, some are "lipophilic", and may cross the blood/brain barrier and cause sedation and possibly seizures (i.e. propranolol). Seizures due to BB should be treated with benzodiazepines and, if required, barbiturates. Other theoretical differences include those that have "membrane stabilizing activity" which may result in cardiac dysrhythmias, and those that have intrinsic sympathomimetic activity which may be protective after acute poisoning.

Are all the CCB alike?

There are three classes of calcium channel antagonists: the phenylalkylamines (verapamil), the benzothiazines (diltiazem) and the dihydropyridines (nifedipine). All effect the slow, voltage dependent calcium channel, however, each have activities at different sites. (Please next column.)

Much of the life-threatening toxicity seen with calcium channel antagonists are due to exposure to sustained-release verapamil or diltiazem. In fact, nifedipine and other dihydropyridines (the newer CCB) rarely require more than volume support for treatment of hypotension and may even exhibit a reflex tachycardia in response to manifested hypotension. Dihydropyridine overdose may also be treated with calcium not unlike the other CCB.

	SA/AV node	vascular tone
phenylalkylamines (verapamil)	+++++	++++
benzothiazines (diltiazem)	+++++	+++
dihydropyridines (nifedipine)	+ / 0	+++++

How did our patient do?

Our patient received orogastric lavage, activated charcoal and whole bowel irrigation. The patient was given 3 grams IV of calcium chloride, after which the blood pressure increased to 110/p mmHG with a heart rate of 60 bpm. She was transported to a tertiary hospital with the ability of invasive cardiac support. En route, the patient required more calcium and arrived with a heart rate of 53 bpm, BP 70/30 mmHg, T 37 C, and RR ("shallow and labored"), the patient was intubated for respiratory support. At this time, an ileus developed and no further GI decontamination could be achieved. The patient received 10 mg of IV glucagon without response. An internal pacer was placed with a resultant heart rate of 80 bpm and dopamine and norepinephrine was added to tailor therapy with invasive hemodynamic monitoring. Over the next 48 hours, the patient was weaned from all therapy, the ileus resolved and the patient regained a full and intact mental status.

References

- Nelson L, Hoffman RS. Effective strategies for drug-induced bradycardia and heart block. *J Crit Illness*.1994;9:916-930.
- Spiller HA, Meyers A, Ziemba T et al. Delayed onset of cardiac arrhythmias from sustained-release verapamil. *Ann Emerg Med* 1991;20:201-203.
- Zaritsky AL, Horowitz M, Chernow B. Glucagon antagonism of calcium channel blocker-induced myocardial dysfunction. *Crit Care Med* 1988;16:246-251.
- Welch CD, Knoerzer RE, Lewis GS. Verapamil and acebutolol overdose results in asystole: intra-aortic balloon pump provides mechanical support. *J Extracorporeal Tech* 1992;24:36-37.

HISTORICAL TID BITS (ANSWERS):

1. Cardiovascular agents
2. 1953
3. chloracne

TOX TRIVIA (ANSWERS):

1. Akee fruit
2. horsetail and bracken fern
3. no effect, nausea and vomiting in large quantities

THE "SPI" CORNER

Topic: Welcome

Welcome to this new component of our quarterly newsletter. Here SPI's will present information that is newsworthy to our practice. What is a SPI you might ask? Specialist in Poison Information is the official title given to nurses, pharmacists or physicians after completing an extensive orientation to the poison control center and the practice of toxicology. The SPI's at the CNYPCC are all nurses and are almost all are "certified" SPI's, meaning that we have successfully handled the required number of cases and have passed a nationally recognized certification examination.

SPI's are not involved in espionage. With the guidance of our toxicologist and medical director, our role is to provide emergency management advice and information to the general public, emergency departments, inpatient units, physicians, nurses, pharmacists, industrial contacts, medical examiners, and even veterinarians in our 14 county coverage area. Our service is provided 24 hours a day, 7 days a week and we are completely confidential. Our annual call volume is 22,000.

We hope you enjoy the SPI corner. Future newsletters may investigate such topics as inhalant abuse, popular overdose of the month, information on current projects of the center, new literature that has changed our practice and trends to watch for. Keep tuned.

Topic: Report from The North American Congress of Clinical Toxicology, Annual Scientific Meeting.

Portland Oregon, Oct. 12-15, 1995

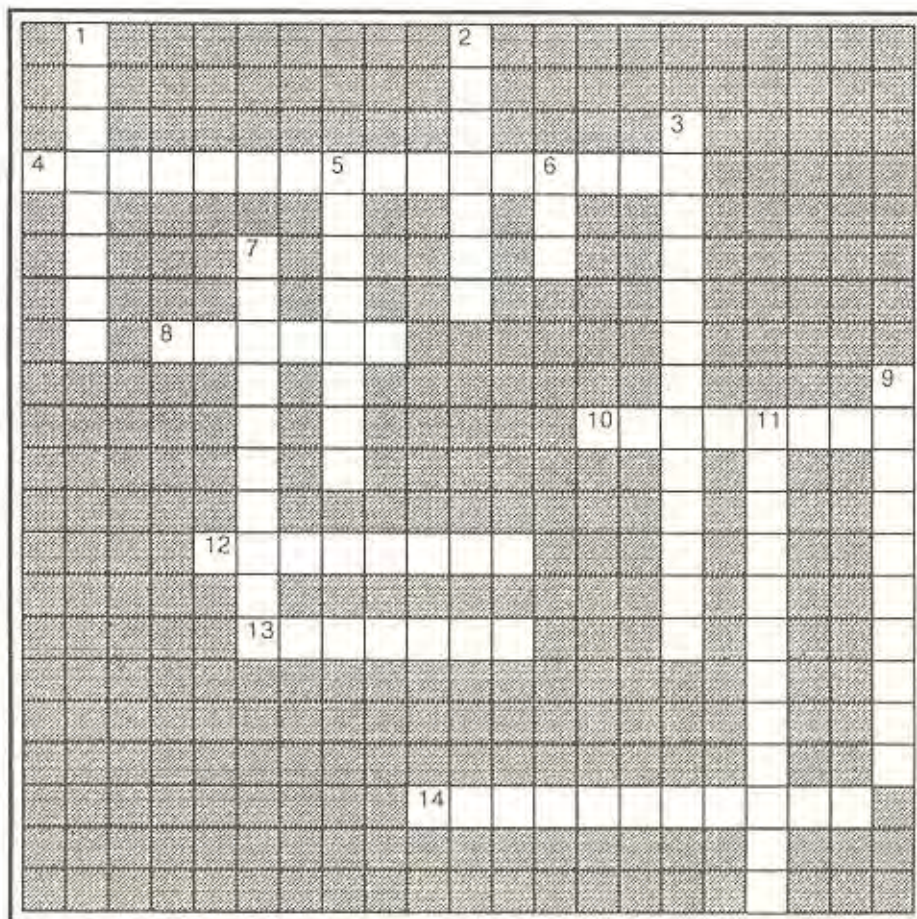
Continuing education at the CNYPCC takes various forms from

weekly case conferences to representation at the North American Congress of Clinical Toxicology Annual Scientific Meeting. The NACCT is an international meeting of toxicologists from all disciplines to discuss the practice of toxicology and to provide a forum for Poison Control Centers to exchange ideas and information. The CNYPCC was represented by an abstract "Pemoline-induced acute choreoathetosis" based on an actual case managed in an area hospital.

I would like to tell you about one symposium of particular interest to me, "What every SPI should know about Poisonings of Cats and Dogs". This workshop provided basic information on the physiology of dogs and cats. Fred Oehme, D.M.V., Ph.D. provided informative and amusing insight into veterinary toxicology. Some veterinary trivia included opioid toxicity in dogs causing central nervous system depression (CNS) while causing CNS excitation in the cat and species variability that exists with greyhound dogs and Persian cats. Some veterinary facts; animals who ingest lead batteries, sinkers, and hazardous construction materials do become lead poisoned and "garbage hounds" often become poisoned by toxins in moldy walnuts and cream cheese. Dr. Oehme also discussed the issue of the malicious poisoning of pets using strychnine and other toxins. This workshop was very interesting considering that we handle approximately 2-3 animal poison exposures a day and in the past have had limited resources. After participating in this workshop, calls on pet owner concerns can be handled comfortably and we can recognize when veterinary consultation is appropriate.

contributed by Marvleen Hollenbeck, R.N., CSPI

ANTIDOTES



ACROSS

- 4 VERAPAMIL OVERDOSE
- 8 CLONIDINE INDUCED LETHARGY
- 10 PHENOTHIAZINE INDUCED DYSTONIA
- 12 CARDIAC GLYCOSIDE TOXICITY
- 13 METHANOL OR ETHYLENE GLYCOL POISONING
- 14 ORGANOPHOSPHATE TOXICITY

DOWN

- 1 RODENTICIDE INDUCED BLEEDING
- 2 CHLORPROPAMIDE OVERDOSE
- 3 METHEMOGLOBINEMIA
- 5 PROPRANOLOL INDUCED BRADYCARDIA
- 6 ACETAMINOPHEN OVER DOSE
- 7 SEIZURES IN A PATIENT WITH TUBERCULOSIS
- 9 VERSED INDUCED APNEA
- 11 IRON POISONING



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Toxicology Letter

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SCHEDULED EVENTS:

S.U.N.Y., H.S.C. Department of
Emergency Medicine

Emergency Medicine Grand Rounds
Marley Education Center: Sulzle Auditorium

Third Friday of the Month, 11:00 AM

April 18 Antibiotics Use in Critical
Illness

May 16 Anesthesia in the Trauma
Patient

June 20 TBA

Toxicology Case Conference

CNYPC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 10:00 AM - 11:00 AM

PROGRAM ANNOUNCEMENT:

Mark your calendar now for CNYPC's first
annual Toxicology Teaching Day in Syracuse
on Wednesday October 29, 1997. More
information to follow !!!

NEWS ALERT:

The Food and Drug Administration has
announced new regulations pertaining to the
packaging of iron preparations. Effective
August 15, 1997 iron supplements must
contain a prominent warning label about the
dangers of excess iron in children and
products containing more than 30 mg of
elemental iron per tablet must be packaged
in unit dose containers.

HISTORICAL TIDBITS:

1. What was the opioid that was used as an
emetic after acute poisoning?
2. Which recently approved antiepileptic's
use was severely limited following reports of
aplastic anemia associated with its use?
3. The first approved use of N-acetylcysteine
was for which disorder?

TOX TRIVIA MATCHING:

(match the solvents with each commonly
used product, may be used more than once)

- | | |
|--------------------------------|--------------------|
| 1. typewriter correction fluid | a. hydrocarbons |
| 2. aerosol paint | b. nitrous oxide |
| 3. airplane glue | c. trichloroethane |
| 4. whip cream propellant | d. toluene |
| 5. magic markers | e. xylene |

CASE HISTORY

Contributed by: Richard Cantor, M.D., FACEP, FAAP

IRON POISONING - FLINTSTONES REVENGE

Two 6 year old children are brought into the Emergency Department after ingesting an unknown amount of prenatal vitamins. They were at school where they shared the vitamins that one child had brought in. The bottle originally contained 50 tablets of Ferrous Sulfate 325 mg, and is now empty. Each child denies exposure. Patient 1 complains of abdominal discomfort, he has had no vomiting or diarrhea. Patient 1 vital signs HR 100/min, BP 90/50 mm Hg, RR 14/min, T 37.8 C. His physical exam is normal except for some epigastric tenderness with no rebound or guarding. Patient 2 has vomited 4 times. His vital signs are HR 110/min, BP 90/p mm Hg, RR 14/min, T 37.5 C. The patient was oriented to person place and time, but appeared sleepy. Physical examination was significant only for the potential change in mental status and voluntary abdominal guarding. Guaiac examination of the stool was positive. Laboratory reports were significant for an anion gap acidosis (AG 24), glucose of 180 mg/dL, and a WBC count of 12,000. Both children had abdominal radiograph's that were negative for radiopacity.

What is the toxic dose of iron?

On a per kilogram basis, the toxic dose of iron must be calculated based on the amount of elemental iron contained in the preparation in question. Most children's multi vitamins are labeled and contain 10-15 milligrams of elemental iron per tablet. Adult preparations, including

Iron Salt	% Elemental Iron
Ferrous Sulfate	20.1%
Ferrous Fumarate	33%
Ferrous Gluconate	11.6%

Ferrous Sulfate, Ferrous Gluconate, and Ferrous Fumarate, contain different amounts of elemental iron based on the percent elemental iron. (please see table 1)

Exposures to elemental iron in doses less than 20 mg/kg are unlikely to result in serious toxicity and asymptomatic patients may be closely monitored in the home setting. Ingestion of doses exceeding 30-40 mg/kg may lead to more serious signs and symptoms of exposure and doses over 60 mg/kg can result in mortality. Both children weighed approximately 30 kg and if one child had ingested all 50 tablets (65 mg elemental iron per tablet), the dose would have been 108 mg/kg.

What is the pathophysiology of Iron Poisoning?

Iron interferes with several cellular processes to cause toxicity. The three organs most involved after iron poisoning include the gastrointestinal, the cardiovascular and the central nervous system. Iron is directly corrosive to gastric mucosal tissue. Initially patients present with nausea and vomiting, however, this corrosive effect may progress

Continued on page 2.

IRON POISONING -continued

to hemorrhagic necrosis and perforation. In the cardiovascular system, circulating iron causes vasodilation, and capillary leak coupled with decreased myocardial contractility. The central nervous system manifestations of toxicity include lethargy and coma, both of which are correlated with the degree of systemic toxicity. In the liver, iron acts as a mitochondrial toxin changing cellular energy metabolism contributing to the production of metabolic acidosis and may lead to subsequent liver failure.

What is the typical clinical course after iron poisoning?

Iron poisoning has been conventionally divided into four phases. These phases are arbitrary, but provide a framework from which to guide the severity of poisoning.

Phase I occurs within 0.5-6 hours after poisoning. Patients present with nausea, vomiting, diarrhea, and gastrointestinal (GI) blood loss. In the most severely poisoned patients, progression may be rapid.

Phase II occurs generally 6 to 24 hours after exposure. Patients stop vomiting during this time period. Clinical evidence of toxicity may be minimal, however, patients that are at risk for progression to the more severe stages of iron poisoning exhibit subtle signs of toxicity, i.e. tachycardia, decreased blood pressure, or depressed mental status. Laboratory evaluation is significant for anion gap metabolic acidosis and elevated iron levels. In very severe overdoses the quiescent phase is absent, with the patient progressing from phase I gastrointestinal symptoms directly to phase III systemic symptoms.

Phase III is characterized by severe systemic manifestations of poisoning including cyanosis and profound metabolic acidosis. Severe cardiovascular toxicity resulting in hypotension and cardiovascular collapse may develop along with severe mental status depression. Multi-system organ failure may develop during this time. This period is typically seen 4-40 hours after exposure.

Gastrointestinal scarring and obstruction has been seen in some patients that go on to survive initial poisoning. This is described as stage IV of poisoning and may be delayed for up to several weeks after initial exposure.

What finding best predicts patients at risk for severe toxicity?

The best predictor for those patients who will develop significant iron toxicity is the presence or absence of vomiting. In those patients that do not vomit within 6 hours after exposure, serious toxicity is unlikely. Those patients that have multiple vomiting episodes or vital sign abnormalities should be closely monitored and evaluated for progression of iron poisoning.

Other, less sensitive markers for iron exposure include iron levels and their correlation with serum glucose and white blood cell (WBC) count. Iron levels taken at peak times after exposure (4-6 hr) have been studied in retrospective trials. Patients with peak iron levels less than 350 mg/dL were at low risk for toxicity, patients with peak levels between 350-500 mg/dL range were at risk for gastrointestinal manifestations of toxicity and patients with peak levels greater than 500 mg/dL were at significant risk for systemic manifestations of toxicity. There are some problems inherent in relying on serum iron levels for the management of the poisoned patient. Levels obtained at times other than the peak are dramatically lower due to a rapid distribution phase and some institutions may not have the ability to quantify iron in a timely manner. Therefore, use serum iron levels as adjuncts, but do not solely rely upon them as markers of poisoning.

The TIBC (total iron binding capacity) theoretically could predict which patients will become ill after iron exposure. It is intuitive that if the serum iron is less than the TIBC, no free iron is circulating and the patient is at very low risk for the development of metabolic acidosis. In vitro studies have shown, however, that the TIBC is falsely elevated in iron overdose and should therefore not be used to guide management of these patients.

Retrospective case analyses of iron poisoned patients have noted that a white blood count > 15,000 and glucose > 150 mg/dL correlated with serum iron levels > 300 ug/dL. Although, when these markers were positive, iron levels were greater than 300 ug/dL, the lack of these markers could not predict that the level was less than 300 ug/dL. The elevations in WBC count and serum glucose are probably a result of stress rather than exposure to iron itself.

What other laboratory tests have value in managing the iron poisoned patient?

Electrolytes and arterial blood gases may be used in the evaluation of iron poisoned patients. These laboratory parameters will be significant for an anion gap metabolic acidosis with appropriate respiratory compensation in the severely poisoned patient. Other pertinent laboratory findings in patients that progress to stage III of poisoning may include increased liver enzymes, increased serum creatinine and abnormal clotting studies.

What decontamination methods are available?

Early, after acute large exposures, syrup of ipecac may be given to induce emesis. The use of syrup of ipecac is rarely required, however, since the earliest sign

HISTORICAL TID BITS (ANSWERS):

- | | |
|----------------|-----------|
| 1. apomorphine | 3. cystic |
| 2. felbamate | fibrosis |

TOX TRIVIA (ANSWERS):

- | | |
|------|----------|
| 1. c | 4. b |
| 2. a | 5. d & e |
| 3. d | |

FOOD POISONING (ANSWERS):

Across:

- Salmonella
- Staphylococcus
- E. coli
- Difficile
- Monosodiumglutamate

Down:

- Yersinia
- Shigella
- Botulism
- Campylobacter
- Scombroid
- Ciguatera

IRON POISONING -continued

of toxicity from iron includes vomiting. Orogastric lavage, using the largest tube size possible may be considered for early large exposures in the hospital setting. However, the relative tablet size of iron may limit the usefulness of orogastric lavage. Iron does not adhere to activated charcoal, severely limiting its usefulness.

Because of the relative lack of gastrointestinal decontamination options in the iron poisoned patient, researchers have investigated various theoretical decontamination solutions. Lavage solutions that have been studied include normal saline, sodium bicarbonate, and deferoxamine, a chelator of iron. The usefulness of all these therapies is theoretical and there is some data that indicates that these therapies may actually be harmful. Therefore, none are currently recommended.

Whole bowel irrigation using polyethylene glycol electrolyte neutral solution (i.e. GoLightly (R), NuLightly (R)) is a relatively recent therapy that may be employed as a mode of GI decontamination. This solution is unique in that it does not result in fluid shifts or electrolyte abnormalities because it does not get absorbed and is electrolyte neutral. The goal of whole bowel irrigation is to wash the GI tract free of toxin before it can be absorbed. The use of whole bowel irrigation has been studied in poisonings where the toxin has delayed absorption or is sustained-release and does not adhere well to activated charcoal. Whole bowel irrigation has been demonstrated to remove residual iron tablets in the gastrointestinal tract and should be considered for all serious ingestions of iron. The dose of the WBI fluid is 2 Liters per hour (up to 500 mL in children) orally and continued until rectal effluent is clear. Many patients will not tolerate WBI without antiemetics and will vomit, especially after iron poisoning. To minimize vomiting, nasogastric administration of WBI solution given as a oral drip and/or antiemetics such as metoclopramide (up to 1-2 mg/kg) or ondansetron should be considered.

Is there an antidote for iron poisoning?

Deferoxamine, the antidote for iron poisoning, chelates free iron. Deferoxamine does not remove iron bound to transferrin or hemoglobin and although deferoxamine does increase iron clearance, 100 mg of deferoxamine binds only 9 mg of elemental iron. Deferoxamine's effectiveness may be related to preventing iron's effects on mitochondria and cellular enzymes. Deferoxamine may be given either intramuscularly (IM) or through continuous intravenous infusion (IV). Indications for deferoxamine include physical findings of anion gap metabolic acidosis, hypotension, or altered mental status (lethargy, stupor, coma, seizures), or a peak serum iron level greater than 500 µg/dL.

The intramuscular dose of deferoxamine is 90 mg/kg up to a maximum of 2 grams every 6 hours. IM doses should be reserved for stable patients in which the progression to more severe toxicity cannot be ruled out. Intravenous deferoxamine is preferred for unstable patients although the IV route carries an increased risk for adverse effects including rate related anaphylaxis and hypotension. The IV dose should be titrated up to 15 mg/kg per hour. The maximum daily dose of deferoxam-

ine is 6 grams due to an association with increased doses and pulmonary toxicity. In severely poisoned patients, however, increased daily doses of deferoxamine should not be withheld. Deferoxamine chelated with iron is a substrate for Yersinia enterocolitidis. Deferoxamine bound to iron that is excreted in the urine imparts a color change that is described classically as vin-rose (or orange to brown). To document a urine color change, a baseline urine specimen should be obtained prior to initiation of chelation.

It is unclear when chelation with deferoxamine can be safely discontinued. A conservative approach is to continue therapy until the urine color returns to normal and the patient is asymptomatic.

Why did our patient receive an abdominal radiograph?

Iron is radiopaque and may be seen on abdominal radiographs, especially if a large amount was ingested, it is adult strength (325 mg) tablets or there is a concretion. Absence of pills, however, does not rule out a serious exposure to iron. Other agents that may be radiopaque are listed on the following table and may be remembered by the mnemonic CHIPES.

C	chloral hydrate, chlorinated
H	halogenated, heavy metals
I	iron
P	packers (illicit drugs), phenothiazines
E	enteric coated
S	solvents, sustained-release

Case

Patient 1 was observed for 6 hours without gastrointestinal manifestations of toxicity and was discharged to home. Patient number two received whole bowel irrigation with antiemetics, fluids for hypotension and was given deferoxamine intravenously at 15 mg/kg/hr. After 24 hours the patient's urine returned to normal color, the anion gap acidosis resolved and the patient regained a normal mental status.

References:

Bosse GM. Conservative management of patients with moderately elevated serum iron levels. *J Toxicol Clin Toxicol* 1995;33:135-140.

Howland MA. Risks of parenteral deferoxamine for acute iron poisoning. *J Toxicol Clin Toxicol* 1996;34:491-497.

Lacouture PG, Wason S, Temple AR et al. Emergency assessment of severity in iron overdose by clinical and laboratory methods. *J Pediatr* 1981;99:89-92.

Tenenbein M. Benefits of parenteral deferoxamine for acute iron poisoning. *J Toxicol Clin Toxicol* 1996;34:485-489.

THE "SPI" CORNER

Contributed By: Nancy O'Neill, R.N., CSPI
Topic: Chloroquine

This topic was chosen because of a marked increase in cases of chloroquine exposure in our service area following operation Desert Storm. Utilization of chloroquine increased primarily in the military service population and likewise most exposures were seen in military based families. As chloroquine is recommended prior to, during and after travel to countries with high incidences of malaria, travelers to those countries will also have ready access to the drug. Once an exposure has occurred, patients with significant chloroquine poisoning should be managed at a health care facility with the ability for advanced cardio-pulmonary life support.

Chloroquine phosphate (Aralen (R)) was originally developed at the end of World War II as an antimalarial for endemic populations. Chloroquine continues to provide effective prophylaxis and treatment for malaria, although some resistance has developed. Malaria is transmitted by the bite of the female *anopheles* mosquito and chloroquine works by eliminating the causative agent, *P. falciparum*. This is accomplished through the inhibition of *P. falciparum*'s ability to synthesize DNA and RNA. Other uses of chloroquine include the treatment of extra-intestinal (hepatic) amebiasis and giardiasis. Chloroquine exhibits some anti-inflammatory effects and has been used for treatment of lupus erythematosus and rheumatoid arthritis.

Chloroquine is generally well tolerated, however, gastrointestinal upset, headache, visual disturbances, vertigo and urticaria have been reported. These effects resolve after discontinuation of chloroquine.

After therapeutic or intentional overdose, changes in mental status and cardio-respiratory status are seen early

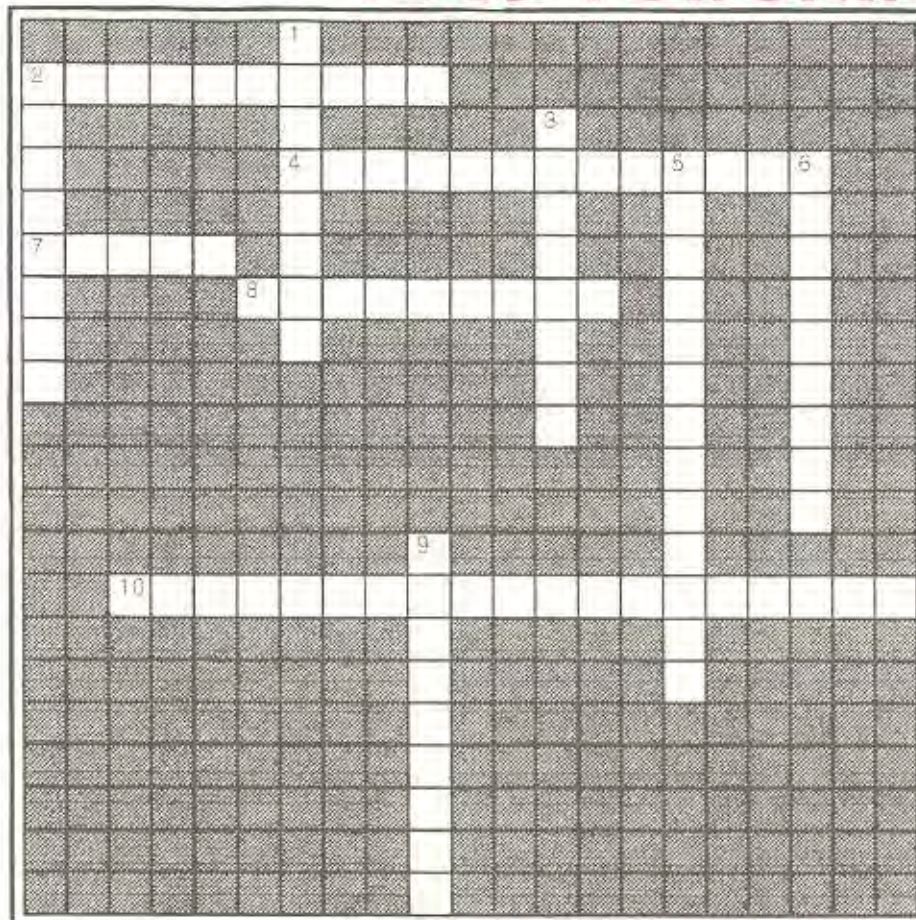
and can be life-threatening. Neurologic symptoms range from hyper-excitability and agitation to delusions, drowsiness, coma and seizures. Sodium channel blocking effects ("quinidine-like") resulting in a widened QRS complex can be seen on ECG along with a multitude of ventricular dysrhythmias. These effects may ultimately result in cardiogenic shock and cardio-circulatory arrest.

Doses that have resulted in death have included 2-3 times therapeutic pediatric doses (8.3 mg/kg orally) within hours after exposure and as little as 2.25 to 3 grams in an adult. Because of the low margin of safety (therapeutic index) associated with chloroquine use, any child or adult ingesting more than a maximum daily therapeutic dose should be evaluated in an acute care facility.

Gastrointestinal decontamination includes the aggressive use of orogastric lavage and activated charcoal. Syrup of ipecac should not be used because of the potential for rapid changes in mental status.

There is no antidote for poisoning resulting from chloroquine exposure. Aggressive supportive measures should be used, including: airway management, intravenous fluids and pressors for hypotension and correction of electrolyte abnormalities. Aggressive use of epinephrine and high doses of diazepam in one study significantly improved outcome. Diazepam has been proposed to be useful for both seizure control and as an antagonist at chloroquine binding sites on the myocardium. Class IA antidysrhythmics (quinidine, procainamide) should be avoided because they likewise block fast sodium channels and may worsen cardiotoxicity. Sodium bicarbonate has been proposed as a treatment and may be used in those patients with a wide QRS complex. Monitoring parameters include frequent ECG and vital sign assessment.

FOOD POISONING



ACROSS

- 2 FROM RAW OR UNCOOKED EGGS
- 4 SHORT INCUBATION PERIOD
- 7 ASSOCIATED WITH HEMOLYTIC UREMIC SYNDROME
- 8 CLOSTRIDIAL INFECTION AFTER PROLONGED ANTIBIOTIC USE
- 10 CHINESE RESTAURANT SYNDROME

DOWN

- 1 NAUSEA, VOMITING, ABDOMINAL PAIN, ARTHRITIS, RASH
- 2 PRODUCES A NEURO TOXIN THAT MAY CAUSE SEIZURES
- 3 CRANIAL NERVE PALSIES, DESCENDING PARALYSIS, HONEY
- 5 UNDERCOOKED POULTRY, MIMICS APPENDICITIS
- 6 MAHI, MAHI, HISTADINE TOXIN, BURNING, INTENSE FLUSHING
- 9 LARGE FISH, RED SNAPPER, DIAPHORESIS, REVERSAL OF TEMPERATURE SENSATION, METALLIC TASTE.



Central
New York
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The CNYPCC

July 1997

Toxicology Letter

Vol. II No. 3

A Quarterly Publication

SCHEDULED EVENTS:

Emergency Medicine Grand Rounds
Marley Education Center: Sulzle Auditorium
Third Friday of the Month, 11:00 AM
Hiatus – July and August, 1997

Oct. 2 – 3, 1997 JB McCabe Visiting Professorship
John McCabe, M.D., FACEP
Vice Dean/Vice President Clinical Affairs
SUNY HSC Syracuse

Toxicology Case Conference
CNYPCC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 10:00 AM – 11:00 AM

PROGRAM ANNOUNCEMENT:

Mark your calendar now for CNYPCC's first annual Toxicology Teaching Day in Syracuse on Wednesday October 29, 1997. More information to follow !!!

CNYPCC TIDBITS:

1. The most common exposure call to the CNYPCC in 1996 was regarding:
a. Plants b. Drugs c. Hydrocarbons
2. _____ % of exposures in the home are referred to health care facilities.
a. 13% b. 90% c. 40%
3. The CNYPCC handles calls related to
a. unintentional drug exposure
b. intentional drug exposure
c. environmental exposures
d. bites and envenomations
e. all of the above

TOX TRIVIA:

1. Two chemicals that have recently been labeled as the date rape drugs are _____, and _____.
2. What two drugs are mixed to make a "Mickey Finn?"
3. What two drugs make up 4's and doors?"

Case History

Contributed by: Kenneth Bizovi, M.D.

INHALATION EMERGENCY

You receive a radio call advising you that paramedics are on the scene with two people. The site is a shoe making factory. Other workers at the site report that the first victim had opened the valve on one of the tanks inside the plant, a rotten egg smell filled the air and he collapsed immediately. The second victim was below and collapsed within a minute. The paramedic states that they have respirators and are preparing to go in after the victims.

What smells like rotten eggs and what is your advice?

Compounds containing sulfur have the smell of rotten eggs. The most likely etiology in this case is sulfur dioxide or hydrogen sulfide. Sulfur dioxide (SO_2) combines with water to form sulfurous acid which is a respiratory irritant. After acute exposure, symptoms include burning, tearing, nasal irritation and cough. Lacrimation, salivation, and wheezing may be noted on physical examination. Large exposures may result in mucosal edema and respiratory compromise. These effects are rarely seen because the onset of symptoms are rapid, causing victims to leave the area of exposure rapidly. The lower airway is typically spared except in overwhelming exposures or when entrapment occurs.

Hydrogen sulfide (H_2S) is a metabolic poison similar to cyanide. Due to its rapid onset, would be rescuers frequently become victims themselves. H_2S is released as a byproduct of many industrial activities including leather processing. Rescuers entering an area of hydrogen sulfide exposure require self contained breathing apparatus (SCBA) as respirators provide inadequate protection.

It would be appropriate in this case to advise rescue personnel to call for HAZMAT backup or entry with SCBA.

Where is hydrogen sulfide found?

Hydrogen sulfide (H_2S) is found in farming, industry, and nature. Putrefaction of sulfur containing proteinaceous material can form pockets of hydrogen gas known as sewer gas or stink dank. H_2S is also one of the components of volcanic gases and is released from sulfur springs. Industries that produce hydrogen sulfide include paper manufacture, production of coke, and nuclear power production. The leather industry uses sodium sulfide in tanning hides. Inadvertent mixture of sodium sulfide with acidic solutions has led to 13 deaths in 2 separate industrial accidents with "scores" of hospitalized victims. Hospital workers have been exposed when cleaning cast room drain pipes with sulfuric acid drain cleaners. Unfortunately, at higher concentrations, H_2S causes olfactory paralysis which prevents any warning that a victim might have had.

INHALATION EMERGENCY (CONT.)

What is the pathophysiology of hydrogen sulfide and what clinical effects occur from exposure?

Hydrogen sulfide reversibly binds to the cytochrome oxidase system, interrupting oxidative phosphorylation leaving only anaerobic metabolism intact. This action leads to the rapid knock down of victims. Death from apnea occurs shortly after exposure if removal from the environment and resuscitation are not rapidly initiated. Although hydrogen sulfide acts similar to cyanide, cyanide binds to cytochrome oxidase with 200 times the affinity and is irreversible. Victims of hydrogen sulfide recover rapidly when removed from the exposure. In fact, cases of victims recovering with shifts in wind direction, are reported. In addition to systemic toxicity, H₂S has irritant properties which result in eye irritation, bronchospasm and pulmonary edema.

The patients arrive at the health care facility. The first victim is in full cardiac arrest, intubated with CPR in progress. The second victim is hypotensive in the field with a depressed mental status. He has improved with O₂ given by a nonrebreather face mask and his initial vitals are BP of 100/70 with a pulse of H₂S. He is mildly confused with a GCS of 14 his lungs are clear to auscultation.

What are the available treatment options?

The primary treatment for hydrogen sulfide is removal from the exposure and the administration of high flow 100% oxygen. Since H₂S exposure results in the lack of usable oxygen, attempts to increase ambient oxygen content also includes the use of hyperbaric oxygen. Cases of patients presenting with pulmonary edema demonstrate benefit after treatment with hyperbaric oxygen. A clear benefit has not been identified in other patient populations exposed to H₂S. The use of hyperbaric oxygen should be considered in patients with ongoing manifestations of poisoning where the risks of hyperbaric oxygen are minimal.

Since the pathophysiology of hydrogen sulfide and cyanide are similar, use of the cyanide antidote kit[®] after H₂S poisoning has been studied. In animals, amyl nitrite and sodium nitrite are effective when administered both prior to and after acute exposure. In these studies efficacy was seen only when nitrates were given within minutes after exposure. There are, cases of nitrates used after human exposure to H₂S, however, no controlled studies are available and it is unclear if patient improvement noted in case reports is solely due to removal from the toxin. Sodium thiosulfate, the third component of the antidote kit has not been studied in humans.

The first victim was treated with sodium nitrite from the cyanide antidote kit. The second victim was placed on a monitor and continued to receive 100% oxygen.

What are other commonly inhaled chemical asphyxiants?

Carbon monoxide

Carbon monoxide (CO) binds to hemoglobin with more than 200 times the affinity of oxygen. This decreases the oxygen-carrying capacity of the blood. CO also causes a left shift of the oxyhemoglobin dissociation curve, prevent-

ing the release of oxygen at the tissue. As 1 CO molecule binds to a hemoglobin tetramer, the binding of oxygen to the 3 remaining heme molecules becomes tighter. As a result, a CO level of 10% will decrease oxygen delivery more than that seen after a 10% decrease in hemoglobin from anemia.

The cardiotoxic effects seen after CO exposure are only partially explained by the decrease in oxygen delivery to the heart. CO binds to myoglobin and poisons mitochondrial cytochrome oxidase to cause direct toxicity. CO is shown to bind to the cytochrome chain in vitro. This binding interferes with aerobic respiration at the cellular level, however, the clinical significance of this is uncertain.

CO is thought to increase free radical formation and lipid peroxidation. This is one of the proposed mechanisms of delayed cerebral edema and delayed neuropsychiatric sequelae seen after CO poisoning.

What are the clinical manifestations of carbon monoxide poisoning?

The clinical signs and symptoms seen after CO poisoning are nonspecific. As with other asphyxiants, the primary targets are the nervous and cardiovascular systems. High concentrations (>100 PPM) cause death within minutes. At low concentrations, patients complain of nausea, headache, and dizziness. There are no specific findings on physical examination or routine neurologic examination. Neuropsychiatric testing can demonstrate memory loss and more subtle decreases in cerebral function, however, this is operator, patient and situation dependent. As neurologic compromise increases, headache may worsen and complaints of difficulty concentrating and weakness occur. Physical examination includes confusion, ataxia, cognitive deficits, and focal deficits. After severe poisoning, coma and seizures can be seen.

Cardiovascular effects occur due to an increased workload to make up for decreased oxygen delivery and direct cardiotoxicity. Cardiac effects seen include palpitations, chest pain, shortness of breath, dyspnea on exertion, tachypnea, and tachycardia. More severe symptoms of ischemia, hypotension and electrocardiogram changes occur after larger exposures. Hemodynamic dysfunction may play a role in the development and exacerbation of neurologic sequelae.

The area of greatest concern in the literature is the ability of CO to cause delayed neurologic sequelae. Neurologic consequences of CO poisoning include personality and memory disturbances, a Parkinson-like disorder, mixed motor sensory peripheral neuropathy, and psychiatric disturbances.

Management of carbon monoxide poisoning

Treatment of CO poisoning involves supportive measures and administration of normobaric or hyperbaric oxygen. Oxygen should be administered as soon as CO poisoning is recognized or suspected. Evaluation for suspected CO can be accomplished by venous or arterial measurement with a co-oximeter blood gas analysis. Pulse oximetry is not useful in the evaluation of the CO poisoned patient because high saturations will be present despite the high CO levels. Oxygen shortens the biologic half-life of CO bound to hemoglobin. On room air the half-life is 3-5 hours, at 1 ATM and 100% oxygen the half-life is 40-90

INHALATION EMERGENCY (CONT.)

minutes and at 2.8 ATM half-life is 20-50 minutes. The implications of the reduction in half-life are unknown.

CO poisoning is also managed using hyperbaric oxygen. Hyperbaric oxygen at 2 or more ATM will increase oxygen delivery and speed CO elimination. Indications for hyperbaric oxygen include altered mental status, neurologic findings, cardiovascular dysfunction, pulmonary edema, severe acidosis, and loss of consciousness. Other criteria for considering HBO include carboxyhemoglobin greater than 25%, history of cardiovascular disease and age older than 60, and pregnancy with symptoms or carboxyhemoglobin level greater than or equal to 15%.

Pregnant patients and infants require special consideration in the setting of CO poisoning. Fetal hemoglobin has a greater affinity for CO, leading to increased effects at a given level in the fetus and infant and a prolonged elimination time. These patients should receive longer treatment with oxygen and should be considered for hyperbaric oxygen with levels greater than 15%.

When should cyanide poisoning be considered?

Combustion of plastics, polyurethane, wool, silk, nylon, nitrocellulose, polyacrylonitriles, rubber, and paper products lead to the production of cyanide gas. In addition to combustion byproducts, cyanide is found in metallurgy, photo processing, and chemistry laboratories. Cyanide is a chemical asphyxiant that interferes with cellular metabolism by binding to the cytochrome oxidase system and halting aerobic metabolism. The actual binding site is the ferric (Fe³⁺) ion on cytochrome A3. The manifestations of poisoned aerobic metabolism are lactic acidosis from anaerobic metabolism and decreased oxygen consumption. Although the mechanism of cyanide poisoning is different from that of CO, the clinical manifestations are quite similar. The central nervous system and cardiovascular system are affected most often, but the signs and symptoms are nonspecific. Central nervous system findings include agitation, cephalgia, disorientation, seizures, coma, and death. Cardiovascular findings include tachycardia, bradycardia, and hypertension that progresses to hypotension with bradycardia and cardiovascular collapse. There is no method for rapid detection of cyanide. The nonspecific clinical findings and the inability to establish definitive diagnosis rapidly is further complicated by the rapid onset and progression of toxicity requiring immediate treatment. Cyanide should be considered in all smoke inhalation victims with central nervous system or cardiovascular findings. The most practical approach would be to assess for other causes of clinical findings such as CO, hypoxia, and hypoglycemia. If no other explanation can be established, treatment for cyanide should be considered. In smoke inhalation victims with CO poisoning,

failure to improve with administration of oxygen may indicate coexistent cyanide and CO poisoning.

Management of Suspected Cyanide Poisoning

Cyanide poisoning is treated using the "cyanide antidote kit." This kit contains three antidotes: amyl nitrite, sodium nitrite, and sodium thiosulfate, in quantity sufficient to treat two adult patients. The nitrites convert hemoglobin to methemoglobin. Cyanide is attracted to methemoglobin and combines to form cyanomethemoglobin. The sodium thiosulfate provides substrate for the enzyme rhodenase, which combines thiosulfate and cyanide to form a non-toxic compound thiocyanate which is rapidly excreted in the urine. The major disadvantage of the nitrites is hypotension secondary to vasodilatation.

The most difficult aspect of treating cyanide poisoning in the setting of smoke inhalation is deciding when to initiate treatment. There is no rapid test for the presence of cyanide. Cyanide levels have been found to be elevated in 78 - 100% of fire fatalities. In one study, 90% of the fire survivors had cyanide levels greater than 0.1 ug/ml. In a fire victim with a CO, inducing methemoglobinemia risks causing a severe decline in oxygen carrying capacity. In this setting, either sodium thiosulfate alone should be given or nitrates with thiosulfate only after the initiation of hyperbaric oxygen.

Several other antidotes for cyanide poisoning are being investigated. Dimethylaminophenol (DMAP) is another methemoglobin-forming agent. Red cells stroma-free methemoglobin, dicobalt, EDTA, and hydroxycobalamin are potential antidotes that act by binding cyanide directly. DMAP is currently used in Europe but not approved in the United States. It may have small advantage over nitrites in that it causes less hypotension and induces methemoglobinemia more rapidly. DMAP still has the major disadvantage of decreasing oxygen carrying capacity. Stroma-free methemoglobin has theoretical concerns about obstruction of renal tubules and allergic reactions. Dicobalt EDTA (Kelocyanor) is currently used in Europe but is not approved in the United States. It chelates cyanide and is excreted in the urine. Side effects include allergic reaction, hemodynamic instability, and tachypnea. The most promising new antidote is hydroxycobalamin (vitamin B12), which is eliminated by the urine. Hydroxycobalamin is considered an orphan drug by the FDA and is used in Europe. Side effects include reddish discoloration of the skin, mucous membranes, and urine, increased blood pressure, and anaphylactoid reactions. If hydroxycobalamin proves to have minimal risk, empiric treatment with sodium thiosulfate and hydroxycobalamin may become the treatment of choice.

Suggested reading

Smith RP, Gosselin RE: Hydrogen Sulfide Poisoning. *J Occ Med* 1979;21:93-97

Reiffenstein RJ, Hultpert WC, Roth SH: Toxicology of Hydrogen Sulfide. *Annu Rev Pharm Tox* 1992; 109-134

Bizovi KE, Leikin JD: Smoke Inhalation among Firefighters. *Occ Med: State of the Art Rev* 1995; 10:721-735

Kirk MA, Gerace R, Kulig : Cyanide and Methemoglobin Kinetics in Smoke Inhalation Victims Treated with the Cyanide Antidote Kit. *Ann Emerg Med* 1993;22:1413-1418

CNYPCC Tidbits Answers

1. b 2. a 3. e

Tox Trivia Answers

1. gamma hydroxybutyrate (GHB) and flunitrazepam (rohypnol)
2. ethanol and chloralhydrate
3. Tylenol #4 (APAP/codeine) and Doriden (glutethimide)

THE "SPI" CORNER

Contributed By: Deborah Anguish, R.N. CCRN
Topic: SSRI Overdose and Adverse Reactions

Selective serotonin reuptake inhibitors (SSRIs) are used as an alternative to tricyclic antidepressants (TCA's) in the treatment of depression. The therapeutic efficacy of SSRIs is equivalent to TCA's in the management of depression with a higher safety margin. The SSRIs include sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), and fluvoxamine (Luvox). SSRI poisoning is less severe than poisoning with TCA's. Common signs and symptoms in the overdose setting include lethargy, nausea and vomiting, anxiety, tremors and tachycardia. Adverse effects and adverse drug reactions associated with the therapeutic use of SSRIs are rare but can be life threatening. One interaction can cause Serotonin Syndrome which is a rare, idiosyncratic drug interaction which can lead to death. Clinicians should be familiar with the causes, signs, and treatment of this syndrome to best identify it and treat patients.

Characteristic clinical manifestations of Serotonin Syndrome include a combination of the following signs; altered mental status (agitation, confusion, disorientation, coma), autonomic dysfunction (blood pressure fluctuation, diaphoresis, hyperthermia, tachycardia), and neuromuscular abnormalities (myoclonus, hyperreflexia,

shivering, and tremor).

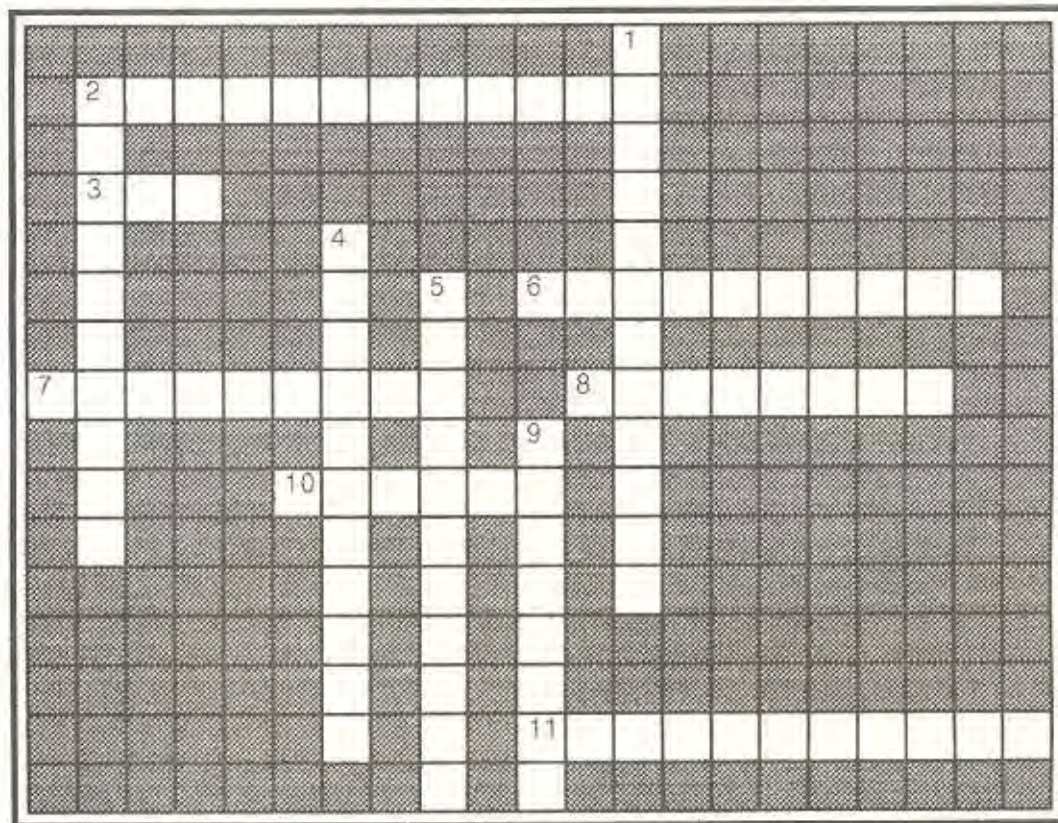
Precipitating events of Serotonin Syndrome include excessive serotonin (5-HT 1A) receptor stimulation, including administration of excess of serotonin precursors or agonists (eg L-tryptophan, LSD, lithium, L-dopa, and buspirone), agents that enhance release of serotonin (MDMA or Ecstasy), and drugs that inhibit the breakdown of serotonin (MAOI).

The symptoms associated with Serotonin Syndrome occur within hours after the precipitating event.

Treatment for Serotonin Syndrome is supportive and aimed at decreasing muscle rigidity, which is thought to be the major contributor to hyperthermia and death. The syndrome resolves in most patients within 24 hrs of removal of the offending drug.

Neuroleptic Malignant Syndrome (NMS), a syndrome caused by a rapid blockade of dopaminergic neuron, appears similar to Serotonin Syndrome in clinical manifestations. The major clinical difference between the two is that signs and symptoms of serotonin syndrome develop within minutes to hours after exposure to the offending agent, whereas NMS typically develops 3-9 days after exposure. Other causes of hyperthermia include malignant hyperthermia, heatstroke, cocaine abuse, anticholinergic reactions, amphetamine use, and use of PCP.

BITES AND ENVENOMATIONS



CLUES: ACROSS

2. MOST COMMON SOURCE OF NECROTIC ARACHNIDISM
3. CLEOPATRA'S INFAMOUS PET
6. BANE OF ADIRONDACK CAMPERS
7. ACCOUNT FOR 90-95% OF POISONOUS SNAKE BITES IN THE US
8. PROMINENT PROBOSCIS, PRURITIC WHEELS, HERALD OF SUMMER IN C.N.Y.
10. NEUROTOXIC PIT VIPER
11. "RED ON YELLOW KILLS A FELLOW, RED ON BLACK VENOM LACK"

DOWN

1. SCORPION SPECIES THAT CAN CAUSE POTENTIALLY SERIOUS HUMAN TOXICITY
2. REDDISH HOURGLASS MARK ON VENTRAL SURFACE
4. BEES, WASPS, HORNETS, AND ANTS
5. RATTLESNAKE INDIGENOUS TO CICERO SWAMP
9. CARRIER OF LYME DISEASE

2. Blackwidow, 4. Hymenoptera, 5. Massassauga, 9. Deer tick
 7. Pitvipers, 8. Mosquito, 10. Mojave, 11. Coralsnakes - Answers Down: 1. Centaurodes,
 BITES AND ENVENOMATIONS - Answers Across: 2. Brown recluse, 3. Asp., 6. Blackflies,



Central
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The CNYPC

October 1997

Toxicology Letter

Vol. II No. 4

A Quarterly Publication

SCHEDULED EVENTS:

Emergency Medicine Grand Rounds

Marley Education Center: Sulzle Auditorium

Third Friday of the Month, 11:00 AM

Oct. 2 - 3, 1997

JB McCabe visiting Professorship:

Speaker: John McCabe, MD, FACEP

Vice Dean/Vice President Clinical Affairs

SUNY HSC Syracuse

October 29, 1997

1st Annual Toxicology Teaching Day

Sheraton University Inn, Syracuse

7:30 AM - 4:00 PM

November 21, 1997

To Be Announced

December 19, 1997

Best Cases of the Year

Toxicology Case Conference

CNYPC, 550 E Genesee Street

Poison Center Conference Room

Every Thursday 10:00 AM - 11:00 AM

PROGRAM ANNOUNCEMENT:

Plan on joining us for the CNYPC's first

annual Toxicology Teaching Day at the

Sheraton University Inn, Syracuse on

Wednesday October 29, 1997. Registration

Now Available; For a brochure please call

315-464-7078

CNYPC TIDBITS:

1. What inhaled toxin was developed around WWI as a chemical weapon that causes profound hemolysis?
2. What was the antidote?
3. What is the most common use of the antidote in the present day management of poisonings?

TOX TRIVIA:

1. What is the smell associated with methane (natural gas)?
2. What is the toxic gas emitted from photocopiers in low quantity?
3. Naloxone (Narcan) can also be useful in some cases of which other poisoning?

Case History

Contributed by: Kathleen Lawless M.D.,
Christine M. Stork, Pharm.D., ABAT

ACETAMINOPHEN (AGAIN ??)

A 61 year old male is brought to the Emergency Department by his wife with a chief complaint of "not acting right". His wife states that he has been a bit depressed lately and has become more sleepy and even difficult to arouse over the past two days. The patient has a history of alcohol dependence and depression. Medications include rauwolfia alkalyoids. Upon arrival, the patient is globally depressed, answering few questions and following simple commands. Vital signs include a temperature of 93.3 F (orally), heart rate of 83/minute, respiratory rate of 32/minute and blood pressure of 96/50 mm Hg. Physical examination is significant for diffuse rhonchi and neurological examination is non-focal with global depression. The patient is given oxygen because of tachypnea and intravenous fluids for hypotension. He is unresponsive to fluids, becomes anuric and is started on dopamine. Initial laboratory results are as follows:

134	91	186	APAP level - 27 mcg/mL
4.8	6	18/4.4	Anion gap = 42
			Arterial Blood Gas: 6.97/17/250/99.1% sat
			Chest radiograph (normal)
			ECG (normal)
PT - 61.3 s, aPTT - 87 s			
ggt - 408 IU/L, ALT - 6647 IU/L, AST - 18,000 IU/L, Alk Phos - 242 IU/L, Bili - 4.5			

How does acetaminophen cause toxicity?

Acetaminophen (APAP) is a common analgesic/antipyretic found as an individual ingredient and in combination with other drugs in a variety of prescription and over the counter products. After therapeutic doses of APAP, the majority of the parent drug is conjugated and excreted in the urine. The conjugation pathways consist of sulfation and glucuronidation with adults exhibiting a greater amount of glucuronidation and children a greater amount of sulfation. Normally, less than 10% of a given dose is excreted unchanged in the urine and less than 5% is metabolized through the CYP2E1 hepatic p-450 enzyme system to n-acetyl-p-benzoquinoneimine (NAPQI). NAPQI is an unstable compound and rapidly combines with available glutathione. Glutathione detoxifies NAPQI which is then excreted in the urine.

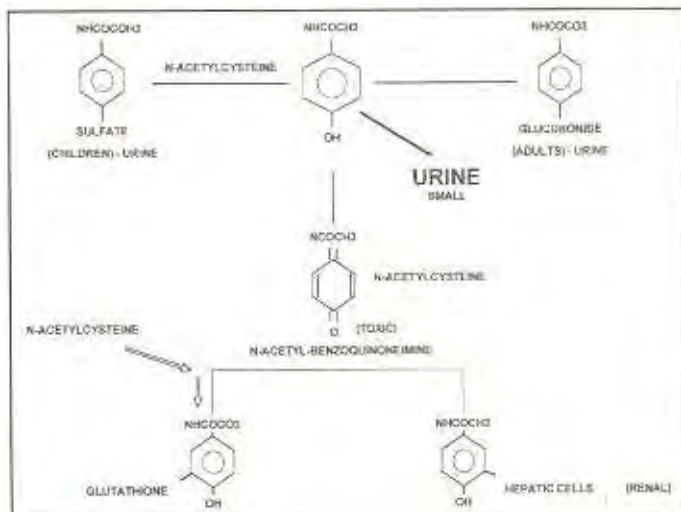
After acute large doses of APAP, the conjugation pathways become saturated. This allows more parent drug to be metabolized to the toxic metabolite, NAPQI. End organ toxicity occurs when glutathione is depleted to less than 30% of original stores. NAPQI is then free to react with hepatic cellular tissue resulting in APAP protein adducts formation and hepatic necrosis. Depletion of glutathione can also occur when supra therapeutic doses of APAP

ACETAMINOPHEN (AGAIN ??)

(CONT.)

are consumed over a long period of time.

Other organs which contain P-450 may manifest signs of toxicity after APAP poisoning. The second most commonly affected organ is the kidney, which is affected in 10% of cases. Rarely, cardiac toxicity is also reported.



What are the stages of acetaminophen toxicity?

After an acute overdose of APAP, toxicity can be classified into four stages as follows:

- Stage 1 – Asymptomatic Period (0-24 hours) During this period, patients experience mild gastrointestinal upset or are completely asymptomatic.
- Stage 2 – Symptomatic Period (24-72 hours) Patients who go on to stage 2 develop right upper quadrant pain coupled with laboratory finding of hepatic insufficiency. (increased liver function tests, PT elevation)
- Stage 3 – Severely Toxic Period (72-96 hours) Patients who go on to stage 3 develop severe manifestations of hepatic insufficiency. Symptoms include jaundice, coagulopathy, altered mental status (coma), renal failure, cardiomyopathy, acidosis and death.
- Stage 4 – Resolution (4 days - 2 weeks) Patients who survive stage three go on to complete resolution of all clinical and laboratory manifestations of toxicity.

Are there medications/habits which may exacerbate acetaminophen toxicity?

As mentioned, the toxic metabolite of APAP is formed through the p-450 iso-enzyme system, specifically CYP2E1. Once NAPQI is formed it is detoxified by combining with glutathione. Toxicity occurs when either there is increased production of NAPQI or when there is a relative lack of glutathione. Many drugs and disease states are capable of altering the NAPQI/glutathione balance to cause an increased risk for toxicity after APAP poisoning. Many of these drugs are also capable of causing hepatotoxicity on their own, providing further reason for caution when using these drugs in combination.

Enhancers of CYP2E1	Glutathione depletion
ethanol – chronic phenobarbital phenytoin isoniazid	excessive APAP dosing chronic liver disease malnutrition – starvation – chronic ethanol

What are the applications/limitations of the Rumack Matthew nomogram?

The Rumack – Matthew nomogram (nomogram) was developed in an attempt to predict hepatotoxicity in patients who present early after APAP overdose. Prior to the development of the nomogram, many patients presenting after acute APAP overdose were not recognized as being poisoned until late when hepatic enzyme elevation occurred or signs of clinical manifestations of poisoning occurred. (See Stages)

After acute overdose, an APAP level plotted at 4 hours or greater on the nomogram can accurately predict patients at risk for hepatotoxicity, defined as SGOT or SGPT > 1000 IU/L. Because of inherent problems of plotting the exact APAP level on the nomogram due to discrepancies in time after ingestion or due to laboratory level deviations, the original nomogram line was reduced 25% from its original value. (See Nomogram) Any patient presenting after APAP overdose who has an APAP level over the nomogram line should receive a full course of the antidote, n-acetylcysteine, (NAC, Mucomist (R)).

How effective is N-acetylcysteine

N-acetylcysteine, given within 8 hours of exposure, is most effective at reducing the risk of chemical hepatitis and virtually eliminates the risk of clinical hepatitis and death. N-acetylcysteine is also effective if used after 8 hours, however, after 8 hours there is a decrease in effectiveness with time. Patients who will not have an APAP level read before 8 hours should receive the first dose of NAC to maximize effectiveness should full course therapy be warranted. NAC can be discontinued once a non-toxic initial level is documented. Once a 4 hour or greater APAP level is accurately plotted on the nomogram and a treatment decision is made, there is no need for subsequent levels.

In cases in which the time since APAP ingestion of APAP is unclear, the longest plausible time should be considered the time of ingestion for purposes of plotting on the nomogram. Also, when chronic doses are ingested over less than a 24 hour time period, the cumulative dose can be plotted as a single dose with the time of the first dose as the time of ingestion. For example, if 8 grams of APAP was ingested since 8 AM and it is now 6 PM, assume all 8 grams were ingested at 8 AM and the time of ingestion was 10 hours ago. This is a conservative approach because subsequently doses contribute to the measured level and because glutathione is being regenerated during this time period.

When the time of ingestion is truly unknown or is greater than 24 hours any APAP level is considered toxic. At 24 hours, the nomogram treatment line approaches zero. In addition, by 24 hours, toxic patients start to exhibit numerical toxicity measured by an elevation in liver function tests (SGOT, SGPT). All of these patients should receive NAC unless their APAP level is zero and their LFT's are normal.

The dose of NAC is 140 mg/kg po as a loading dose followed by 70 mg/kg po every 4 hours for a total of 18 doses. Supplied NAC should be diluted to a 5% concentration before administration.

ACETAMINOPHEN (AGAIN ??)

(CONT.)

How does N-Acetylcysteine attenuate acetaminophen toxicity?

NAC acts as a precursor to glutathione. (See figure) As glutathione is regenerated, more is available to bind with NAPQI to prevent its binding with hepatocytes. N-acetylcysteine is also effective in the later stages of APAP toxicity, even after all available APAP is metabolized. There are several reasons why NAC is helpful later in poisoning. NAC supplies sulfhydryl groups, enhances microcirculation and cardiac output, and is a very powerful antioxidant. Clinically, the use of NAC late in poisoning is shown to reduce mortality by as much as 50%. Although, standard dosing of NAC is an 18 dose course, in these cases, NAC should be continued until there are objective signs of improvement, the patient dies or the patient received liver transplantation.

What are the APAP poor prognostic indicators?

Several studies have been conducted to identify patients who are at risk for death after APAP poisoning. Early recognition of these patients facilitates patient transfer to a transplant center and promotes ultimate patient survival. It is also important to identify those patients who will do well without transplant because the long term morbidity and mortality after APAP overdose is negligible.

The poor prognostic indicators center around measures of synthetic hepatic function. Poor mental status, renal function and coagulation together, acidosis alone, or absence of formation of synthetic factors have been identified to correlate with poor outcome. (See table)

Poor prognostic indicators after APAP Overdose

Serum creatinine > 3.3 mg/L
Grade III-IV encephalopathy
PT greater than 1.8 X control

pH < 7.3 after fluids

factor VIII/V ratio > 30

What are the adverse effects associated with N-acetylcysteine?

NAC smells like rotten eggs produces a significant amount of nausea and vomiting when given orally. To limit vomiting, the proper dilution of NAC should be assured. Other techniques include placing NAC in an opaque covered container to minimize smell or giving NAC through a slow nasogastric infusion thereby minimizing gastric distention. Lastly, antiemetics can be given. An optimal antiemetic does not reduce gastrointestinal motility so that further NAC doses can be safely administered. Commonly recommended antiemetics include metoclopramide (up to 1-2 mg/kg) and ondansetron (0.15 mg/kg).

Intravenous NAC is not currently available in the United States, although it is routinely used in other countries. The

intravenous formulation is rarely associated with anaphylactic reactions. The US product for oral use is sterile, but not assured to be pyrogen free. In rare cases such as when gastrointestinal integrity is impaired, the oral product can be given intravenously.

What is the significance of the activated charcoal/N-Acetylcysteine interaction?

Activated charcoal is useful early after acute APAP overdoses. The aggressive use of activated charcoal can obviate the need for NAC through limiting the amount of APAP absorbed, and thereby decreasing the measured APAP level. When activated charcoal is given at the same time as NAC, some of the antidote is adsorbed to the activated charcoal. The decrease in bioavailability of NAC is estimated at 30%. The impact of this interaction is minimal when taken in context. For example, the dose of NAC given after APAP overdose is the same whether the 4 hour APAP level is 150 mg/L or 400 mg/L. This indicates that the usual dose of NAC provides more than enough antidote to treat both situations. Also, in most cases an additional 17 doses of NAC will be given without activated charcoal, limiting any further interaction for the majority of NAC dosing. In those cases in which co-ingestants warrant multiple doses of activated charcoal, it is prudent to stagger the doses of activated charcoal with those of the NAC in order to minimize the interaction.

What is the extended relief (ER) formulation of acetaminophen?

Recently, an extended relief (ER) version of APAP was released. This preparation is composed of a bi-layer in which the outside layer is penetrated easily, and an inner layer penetrated slowly, thereby delaying absorption. The product formulation strength is 650 mg and is meant to be given every 6-8 hours.

The interpretation of the nomogram levels after an acute overdose of ER APAP is unclear. The nomogram was developed using data obtained after acute overdoses of regular release (RR) formulations of APAP. Healthy human trials of ER APAP compared to RR APAP demonstrated a lower peak concentration and a delay to the time to peak concentration with the ER preparation. It was unclear if elimination rate was changed in these trials. Several have reported cases in which APAP levels crossed the nomogram line after initially being read as non-toxic. A conservative approach to these patients is best until more information is available. In these patients two APAP levels separated by at least 4 hours underneath the nomogram line should exclude patients with potential for toxicity.

How did our patient do?

The patient was admitted to the intensive care unit where the spouse offered additional history of finding an empty bottle of APAP 48 hours earlier. The patient continued to receive N-acetylcysteine while a liver transplant consult was initiated. Despite aggressive supportive care, the patient deteriorated rapidly and expired after a massive gastrointestinal bleed.

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CNYPCCTidbits Answers

1. Arsine Gas (AKA lewisite)
2. BAL (British Antilewisite)
3. Lead Poisoning

Tox Trivia Answers

1. There is no smell from methane. The smell of leaking gas is from added mercaptans in order to identify the presence of a leak
2. Ozon
3. Clonidine, valproic acid

THE "SPI" CORNER

Contributed By: Deborah Anguish, R.N., Michele Caliva, R.N. CSPI, Pat Koniz, R.N. CSPI

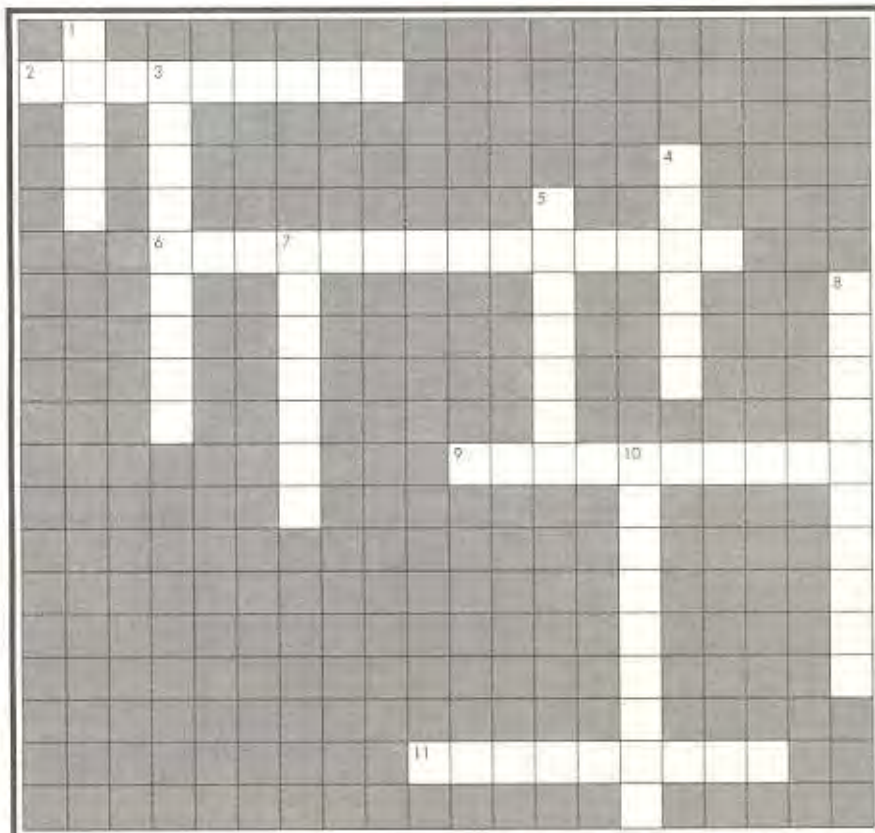
Many times each year, the poison control center recommends the use of an antidote after a poison exposure. At the Central New York Poison Control Center, we compile an updated list of all the available antidotes at the 32 hospitals in our service area. A yearly survey is completed by each hospital pharmacy with a checklist of suggested antidotes. This survey allows the poison control center to keep track of the regional and local availability of important antidotes. If you are in need of an antidote that your pharmacy does not carry or if you need more antidote than your pharmacy has available, the poison control center specialists can identify the nearest location and arrange for the transport of the antidote to your facility. The monitored antidotes in our 14 counties include:

N-Acetylcysteine	Activated Charcoal	Antivenin
Atropine	Bicarbonate	Calcium
Ca EDTA	Cyanide Antidote Kit	Deferoxamine
Digoxin Fab Fragments	Dimeric caprol	Glucagon
Syrup of Ipecac	Magnesium	Mannitol
Methylene Blue	Naloxone	Nicotinamide
Penicillamine	Physostigmine	Pralidoxine
Protamine	Pyridoxine	Vitamin K1

The CNY PCC receives over 5,000 calls from hospitals each year. One of the many questions health care providers ask concerns the use of flumazenil after acute benzodiazepine overdose. Due to its controversial use, often times the Specialist in Poison Information will consult with one of the toxicology consultants before recommending its use. The routine management of benzodiazepine overdose includes gastric decontamination with activated charcoal and supportive care. Benzodiazepines are agonists at the benzodiazepine receptor site causing anticonvulsant, sedative and muscle relaxant effects. Antagonist, such as flumazenil competitively occupy this site.

One of the risks involved with the generic use of flumazenil is precipitating acute withdrawal symptoms (including seizures) in patients chronically using benzodiazepines. Additionally, flumazenil should be used with caution when epileptogenic drugs may have been ingested. A partial list of drugs that may cause seizures include; cocaine, isoniazid, lithium, theophylline, carbamazepine and tricyclic antidepressants. Because benzodiazepines rarely cause significant morbidity and mortality and the use of flumazenil may result in life-threatening complications, the routine use of flumazenil is rarely indicated.

TOXIC PLANTS



CLUES: ACROSS

- The brilliant colored beans of this plant, when chewed, can cause delayed gastroenteritis, CNS depression, shock and death
- Also called dumbcane – contains calcium oxalate crystals that, when released when chewing, cause irritation of the mouth and throat
- Popular at Xmas – thought to be toxic, yet only causes mild irritation to the skin and GI tract
- Can cause anticholinergic hallucinations; used by Cleopatra to woo Caesar

DOWN

- Popular at xmas, the bright berries of this plant can produce nausea, vomiting, and diarrhea with significant dehydration and electrolyte imbalance
- A substance found in peach and apricot pits, produces hydrocyanic acid (cyanide)
- This common houseplant will not "bite" – it is non toxic
- The bulb of this springtime flower, if ingested, can produce N/V/D, usually only requiring supportive care
- A source of digoxin production
- Although the leaves and buds contain a cyanogenic glycoside, in most reported poisonings, only GI symptoms have been seen
- The ingredient in Black Nightshade, as well as the leaves of tomato plants, that causes N/V/D, headache, and muscle weakness

TOXIC PLANTS – Across: 2. Rosarypea; 3. Amygdalin; 4. Spider; 5. Daffodil; 6. Foxglove; 7. Hydrangea; 8. Solanum; 9. Poinsettia; 10. Jimsonweed; 11. Holly; 12. Solanum