

Central  
New York  
Regional  
Poison  
Control  
Center

The CNYPC

April, 2000

# Toxicology Letter

Vol. V No. 2

A Quarterly Publication

## SCHEDULED EVENTS:

Emergency Medicine Grand Rounds

### NEW LOCATION & DAY:

Health Sciences Library Room 318

Second Wednesday of the Month, 11:00 AM

April 12; May 10; and June 14, 2000

Toxicology Case Conference

CNYPC, 550 E Genesee Street

Poison Center Conference Room

Every Thursday 10:00 AM – 11:00 AM

and every third Thursday 1 PM to 2 PM

## PROGRAM ANNOUNCEMENT:

Please mark your calendars now and plan to attend our Fourth Annual Toxicology Teaching Day. We are planning an exciting line-up of lectures and workshops as well. The date is Wednesday November 1, 2000. A flyer will be coming shortly. Please call 464-7078 for more information.

## CNYPC TIDBITS:

Match the toxin with the antidote:

- |                             |                       |
|-----------------------------|-----------------------|
| 1. ethylene glycol          | a. sodium nitrite     |
| 2. cyanide                  | b. sodium bicarbonate |
| 3. chloral hydrate          | c. propranolol        |
| 4. tricyclic antidepressant | d. ethanol            |

## TOX TRIVIA:

1. Which live species is not reported to contain a toxin? (snails, snakes, spiders, squirrels, birds)
2. Which is not a source of carbon monoxide? (furniture stripper, furnace, car, household iron)
3. True/False: Preformed toxin ingestion of botulinum is responsible for the majority of toxicity in infants.

## Case History

**Contributed by:** Jennifer Falchek, Pharm.D. Candidate, Christine M. Stork, Pharm.D., ABAT

### HYPOGLYCEMIC POISONING

#### Case:

A 75 year old male ingests all of his oral hypoglycemics in a suicide attempt. After 45 minutes, and in Emergency Care, he is alert and oriented with a heart rate of 75/minute, blood pressure of 150/85 mm Hg, respiratory rate of 14/minute, and temperature of 37 C (orally). Further history reveals that the patient is missing metformin (Glucophage) tablets.

#### What is the therapeutic role of metformin?

Metformin (Glucophage) is a biguanide oral hypoglycemic that exhibits antidiabetic effects through several pharmacologic mechanisms. Metformin enhances peripheral muscle glucose uptake, inhibits glucose release from the liver, and decreases intestinal glucose absorption. Metformin is considered most commonly as second line therapy and is therapeutically used in conjunction with another antidiabetic pharmaceutical.

Another antidiabetic of the biguanide class, phenformin was removed from the US market in 1976 due to a high risk of lactic acidosis (64 cases/100,000 patient years). This is due to the ability of phenformin to inhibit mitochondrial lactate utilization in addition to the pharmacologic effects noted for metformin. Phenformin cases of lactic acidosis may still occur in the US when patients receive medications from other countries. In particular, metformin is still available in Canada, Europe, and South America.

Metformin undergoes little mitochondrial binding. Lactic acidosis is seen, however, in approximately 3 cases/100,000 patient years. The mechanism thought related to metformin induced lactic acidosis includes decreased gluconeogenesis from alanine, pyruvate, and lactate leading to lactate accumulation. The risk of metformin associated lactic acidosis is increased with concurrent renal insufficiency and therefore the drug should not be used in these patients.

#### What are the consequences of metformin in the acute overdose setting?

There are few large case series detailing acute overdoses of metformin. Small case series suggest a risk of lactic acidosis

## **HYPOGLYCEMIC POISONING (CONT.)**

without hypoglycemia. When lactic acidosis occurs in patients using therapeutic doses of metformin, it is considered life-threatening because reported case series demonstrate a death rate of approximately 50%. It is unclear how this finding should be extrapolated to the acute overdose setting. Hypoglycemia was only seen in patients with concurrent ingestions of insulin or sulfonylureas. Other symptoms reported in scant case reports include lethargy and disseminated intravascular coagulation (DIC). Patients who are not diabetic presented with symptoms of GI complaints, headache, and dizziness. A single case series of children with reports of accidental metformin exposure found no significant health risk of hypoglycemia and no evidence of lactic acidosis.

### **What other antidiabetic is this patient likely to have access to?**

As metformin is a second line agent in the treatment of diabetes, it is likely that this patient has access to other commercially available antidiabetics, most of which are considered direct hypoglycemics. A list of currently available antidiabetic agents is seen on Table-1. A unique plant source of hypoglycemia is the Ackee fruit that is eaten in Jamaica. It has been reported to cause Jamaican vomiting illness when the unripe fruit, containing excess concentrations of the toxin, hypoglycin A, is consumed.

### **What are the manifestations of sulfonylurea overdose? Are there any patients at particular risk?**

The sulfonylureas stimulate insulin release from pancreatic  $\beta$ -islet cells, reduce glycogenolysis, and increase insulin receptor sensitivity. The sulfonylureas, unlike the biguanides, lower blood glucose in normal patients. Children are very susceptible to sulfonylureas. There are case reports and retrospective case series of a single tablet causing hypoglycemia and although not confirmed in prospective case series, the onset of hypoglycemia in these children was reported to be substantially delayed.

### **Is there any way to tell whether this patient administered insulin?**

The physical examination of a patient injecting insulin can be normal or may reveal a erythematous, boggy, hemorrhagic, and painful site.

The injection site can serve as depot for continuous insulin release. In addition, measured insulin levels should be elevated in the presence of hypoglycemia. C-peptide levels can be used as a quantitative marker to differentiate between endogenous insulin over production or release because unlike exogenous insulin, endogenous insulin is a proinsulin, cleaved to form insulin plus C-peptide. Another technique for determining the use of exogenous insulin is the presence of insulin binding antibodies, generally only present in patients using exogenous insulin.

### **What about the newer drugs? Are the thiolidinediones such as troglitazone, piaglitazone, and rosiglitazone toxic?**

There is little information regarding overdose with the thiolidinediones. Overdose information is derived from adverse effects at therapeutic levels. Although infrequently reported, hypoglycemia can occur, especially when used in a poly-drug regimen. Reports of hepatotoxicity occur after therapeutic troglitazone therapy, but long-term studies especially on the recently released agents are lacking.

### **How long do we need to monitor this patient?**

Due to the risk of poly-drug regimens and the lack of information regarding acute metformin overdose in adults, this patient should be monitored for 24 hours even if asymptomatic.

### **Are there any special antidotes we can use?**

Glucose is the mainstay of therapy for hypoglycemia. It can be administered intravenously then orally when food is tolerated. Intravenous glucose should be given at a rate to keep the patient euglycemic, in order to prevent further insulin release and subsequent hypoglycemia. Regulators of insulin secretion that are available in cases not responding to caloric increases include diazoxide (Hyperstat<sup>®</sup>) and octreotide (Sandostatin<sup>®</sup>). Diazoxide directly inhibits insulin secretion by opening  $K_{ATP}$  channels. Because of adverse effects of sodium retention and hypotension and increased effectiveness with octreotide in simulated overdose models, octreotide is considered the insulin modular of choice. Octreotide inhibits glucose-stimulated  $\beta$ -cell insulin release through a G coupled protein.

**HYPOGLYCEMIC POISONING (CONT.)**

**Table-1 Currently Available Antidiabetic Drugs**

CLASS	GENERIC	BRAND	INSULINS:	
			TYPE	BRAND NAME
Sulfonylureas	acetoexamide	Dymelor®	Short-acting  very short-acting  regular   Intermediate-acting  NPH   Lente   NPH/Regular mixtures   Long-acting Ultralente	Humalog®  Regular Iletin I & II®  Humulin R®  Novolin R®   NPH Iletin I®  Humulin N®  Novolin N®  Lentin Iletin I & II®  Humulin L®  Novolin L®  Humulin 70/30®  Humulin 50/50®  Novolin 70/30®  Humulin U®
	chlorpropamide	Diabinese®		
	tolazamide	Tolinase®		
	tolbutamide	Orinase®		
	glimepiride	Amaryl®		
	glipizide	Glucotrol XL®, Glucotrol®		
	glyburide	Micronase®, Glynase®, Diabeta®		
Thiazolidinedione	troglitazone	Rezulin®		
	rosiglitazone	Avandia®		
	piaglitazone	Actos®		
α-glucosidase inhibitor	acarbose	Precose®		
	meglitinide			
	repaglinide	Prandin®		

After chlorpropamide overdose, urinary alkalinization using sodium bicarbonate can be used to increase excretion.

Lactic acidosis, associated with biguanide therapy, is treated with sodium bicarbonate and hemodialysis, resulting in rapid improvements in acid-base status and removal of metformin from the blood. Persistent lactic acidosis and/or recurrent lactic acidosis is reported and should be monitored for. Along with these options, supportive care is required for all oral hypoglycemics overdoses.

**CNYPCC Tidbits answers**

1. d
2. a
3. c
4. b

**Tox Trivia answers**

1. squirrels
2. household iron
3. False, Clostridium botulinum and formed toxin cause toxicity

**Patient Follow-up**

The patient maintained a blood glucose >90 over 24 hours with no exogenous intravenous glucose required. Initial electrolytes were normal with a serum creatinine of 1.4 mg/dL. Renal lactate measurements revealed an increase of 6 u/L up to 25 u/L, but not outside the therapeutic range and serum bicarbonate remained normal throughout.

**Select References:**

Quadrani DA et al. Five year retrospective evaluation of sulfonylurea ingestion in children. J Toxicol Clin Toxicol 1996;34:267-270.

Spiller HA et al. Multicenter case series of adult metformin ingestion.(abstract) & Multicenter case series of pediatric metformin ingestion.(abstract) J Toxicol Clin Toxicol 1999;37:639-640.

Boyle PJ, Justice K, Krentz AJ et al. Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. J Clin Endocrinol Metab 1993;76:752-756.

**THE "SPI" CORNER – TOPIC: CARBON MONOXIDE**

**Contributed By: Nancy O’Neil, R.N., CSPI**

Carbon monoxide (CO) forms as a result of the incomplete combustion of carbon containing material. Some examples of sources of exposure include exhaust from malfunctioning furnaces, gas kitchen stoves and automobiles. Furniture stripper, methylene chloride, is converted to CO in vivo.

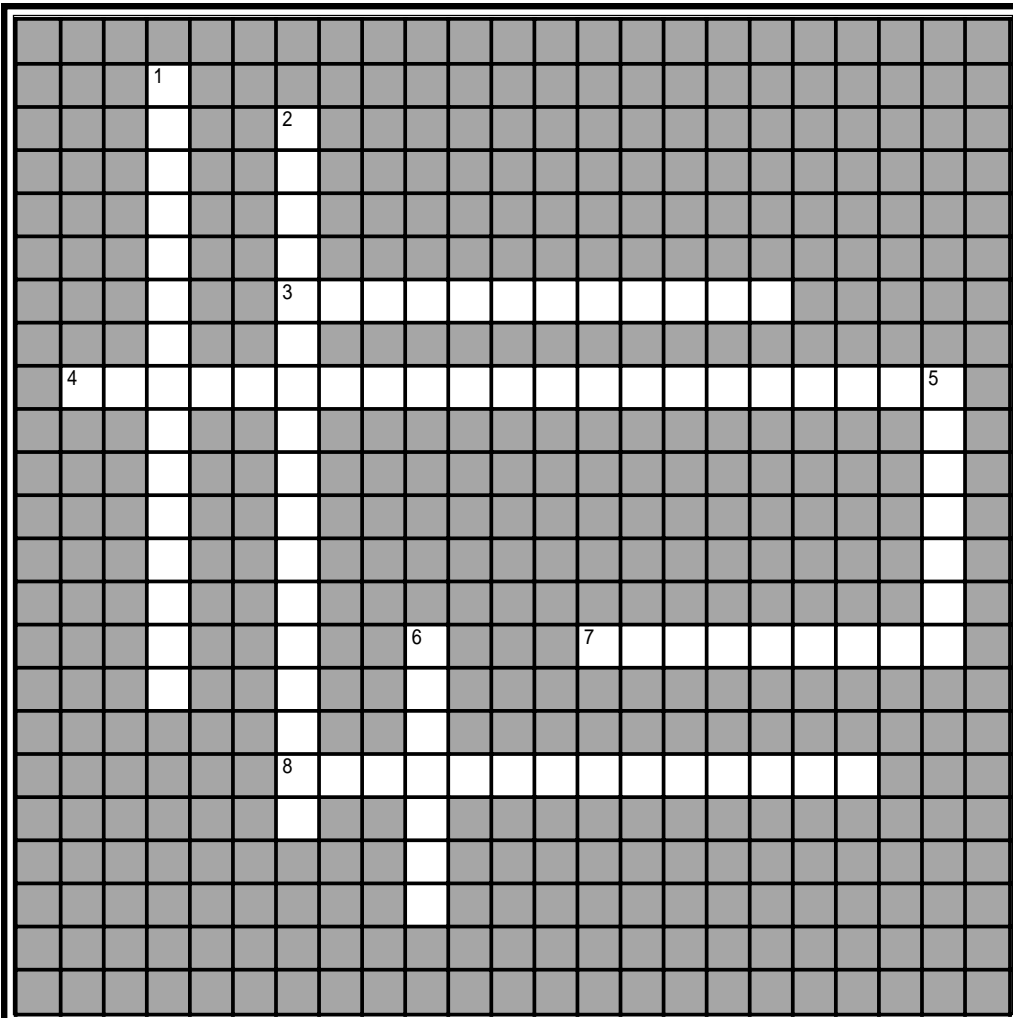
Acute toxicity from CO results in impaired oxygen delivery and utilization, which leads to cellular hypoxia. Initial symptoms may be easily confused with a variety of other medical illnesses. Typical manifestations of acute mild poisoning consist of lethargy, headache, dizziness and nausea. Moderate effects include chest pain, blurred vision, dyspnea on exertion, tachycardia, tachypnea, cognitive defects and ataxia. Severe poisoning results in seizures, coma, dysrhythmias, hypotension, myocardial infarction and death. CO levels are very loosely associated with manifestations of CO poisoning, with any level >10% indicating significant exposure. Persistent delayed effects seen after significant CO poisoning can include dementia, amnesic syndromes, psychosis, parkinsonism, chorea,

cortical blindness, peripheral neuropathy and incontinence.

Patients at particular risk include those with increased respiratory rates such as children, and pregnant patients. Fetal hemoglobin binds more efficiently and longer to CO, placing those patients at excessive risk.

Treatment of CO poisoning includes removal from the environment, oxygen and in some cases hyperbaric oxygen therapy. Oxygen decreases the half-life of CO that is acting on red blood cells. Hyperbaric oxygen further decreases the half-life of hemoglobin bound CO and may, in addition, provide protection from severe delayed manifestations for those at risk. Patients who should be considered for hyperbaric oxygen therapy include moderate-severely poisoned patients and patients with elevated levels >20-25%.

Prevention includes proper installation and maintenance of appliances. In addition, commercially available CO detectors are exquisitely sensitive, even to low levels of CO in the atmosphere, and provide an early warning that a source of CO is in the area.



**CAUSES OF SPRING FEVER (HYPERTHERMIA)**

Contributed by; Deborah Anguish, RN, CSPI

CLUES:  
DOWN

- 1. Blind as a bat, mad as a hatter, dry as a bone
- 2. Drug interaction, usually involves SSRI's, or MAOI's
- 5. Over the counter pain and fever reducer
- 6. Powder of abuse

ACROSS

- 3. Too much of the older medication, replaced by Synthroid®
- 4. Rare inhalational anesthetic reaction
- 7. Microbial or viral
- 8. Inhalation of burning metals

Across: 3. Thyroid storm, 4. Malignant hyperthermia, 7. Infection, 8. Metal fume fever  
Down: 1. Anticholinergic, 2. Serotonin syndrome, 5. Aspirin, 6. Cocaine