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6/07

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Section A

To: Directors of Pharmacy, Directors of Medicine, Emergency Medicine,
Critical Care, Pediatrics and VPs Nursing
From: Bruce Ruck, Pharm.D.
Date: 3/25/07
Re: n-acetylcysteine IV (Acetadote®) and n-acetylcysteine PO (Mucomyst®)

Attached you will find the latest information to be added to the NJPIES Poison Management binder which was sent to all Directors of Pharmacy in April 2002 and last updated Sept, 06. This update contains information on the use of n-acetylcysteine IV (Acetadote®, the only US FDA licensed IV preparation) and PO (Mucomyst®).

Prior to the availability of Acetadote®, the staff of NJPIES, like many poison centers, suggested that the oral/inhalation formulation of n-acetylcysteine (NAC) available at that time may be given IV when necessary. While the need to administer the oral formulation IV rarely arises today, we have included information on this product as well.

The attached fact sheets are designed to answer common questions we receive regarding the use of these products and hopefully help in promoting safe, rational, pharmacotherapy.

In addition, we also suggest that each hospital stock enough of the new product Acetadote® to treat 3 patients at a time. While the average patient will be treated with 4 vials, some may need more because the dose is on a mg/kg basis. In addition some patients may require greater than the typical 21 hour infusion, because they have evidence of hepatic damage caused by acetaminophen.

While we are sending copies of this to other health care professionals in your institution, please check our distribution list and forward this document to others you deem appropriate.

Please let me know if we can be of assistance with this or any medication related question. Just a reminder, Drug & Poison information calls should be directed to 800-222-1222, administrative matters to 973-972-9280

New Jersey Poison Information and Education Fact Sheet

What is the difference between Acetadote® IV and Mucomyst® Oral?

- Acetadote® is the only FDA approved **intravenous** formulation of n-acetylcysteine (NAC) indicated for the prevention of hepatotoxicity following an acetaminophen overdose.
- Mucomyst® and the generic versions of it also contain NAC and when used via the oral route, it is also indicated for the prevention of hepatotoxicity following an acetaminophen overdose.
- The major difference in products is the FDA approved labeling and the guarantee that the IV formulation is sterile and pyrogen free.

Must we switch our method of treating an acetaminophen overdose from oral NAC to IV NAC?

- No, one can continue to treat with oral NAC when clinically appropriate. In most situations there is no advantage of the parenteral NAC vs oral NAC.
- NJPIES still suggests oral NAC in most of the acetaminophen exposures we are asked to consult on. Below are examples where we still suggest oral NAC
 - patient presents relatively early after a suspected acetaminophen overdose (< 12 hours post ingestion)
 - patient is not nauseated or vomiting
 - laboratory data suggesting no hepatic abnormalities
 - AST/ALT/INR all within the institutions normal range

When would NJPIES suggest IV NAC (Acetadote®)?

- IV NAC can be used in place of oral NAC whenever the clinician determines it is best for the patient. However, NJPIES most often suggests it when:
 - The patient is nauseated or vomiting
 - The patient presents with laboratory data suggesting a late presentation. I.e., hepatic abnormalities
 - Elevation in AST/ALT/INR
 - The patient presents after a chronic exposure
 - Has taken several grams over several hours to several days (see late presentation below)

What are the benefits of IV administration versus oral administration?

- IV administration prevents the delay of NAC administration often seen if the patient is experiencing nausea or vomiting
- IV administration may decrease the need for anti-emetics and avoid the cost and side effects associated with anti-emetic therapy
- IV NAC can be given without regard for the administration of activated charcoal or for whole bowel irrigation (WBI) when a mixed overdose is suspected and WBI is indicated

Why has NJPIES suggested IV NAC in those that present "late" after exposure with elevated liver enzymes vs oral administration?

- With those that present "late" after exposure one tries to limit the progression of both hepatotoxicity as well as toxicity to other organs. After intravenous administration, higher blood levels are achieved delivering more NAC to other organs and theoretically decreasing the risk/progression of systemic toxicity. The only scientific data that exists regarding the efficacy of NAC in late-presenting cases of acetaminophen overdose is based on IV use of the antidote.

What adverse effects have been associated with IV NAC?

- The most commonly reported adverse events are rash, urticaria, and pruritis, occurring at a frequency of 0.2%-20.8%. This reaction appears to be a “rate related” anaphylactoid and occurs most often during the loading dose of IV NAC.
 - This reaction is not immune based and not considered an “allergy”
 - To decrease the risk of this reaction, the loading dose should be given over ONE HOUR, not 15 minutes as originally approved by the FDA
- While anaphylactoid reactions result in similar clinical findings as an “allergic reaction,” slowing the rate of administration often decreases the risk of recurrence
- The following anaphylactoid reactions have been described with IV NAC
 - Rash
 - Flushing
 - Erythema
 - Vomiting
 - Hypotension
 - Wheezing and/or shortness of breath
- Acute flushing and erythema of the skin has been reported to resolve spontaneously even with continued use; however one may wish to hold the infusion until symptoms dissipate and then restart the infusion at a slower rate
- Symptoms of anaphylactoid reactions can also be treated with antihistamines
- Caution is advised when administering to patients with asthma or history of bronchospasm.

Why does the package insert indicate administration of IV NAC within 8-10 hours after ingestion of a potentially toxic APAP dose?

- The sooner NAC (IV or PO) is administered after the ingestion of a potentially hepatotoxicity dose of acetaminophen the less risk of developing hepatotoxicity. Administration within 8-10 hours virtually eliminates the likelihood of any toxicity.

If a patient presents to the hospital > 8-10 hours after a suspected acetaminophen overdose would IV NAC be of any benefit?

- Either oral or intravenous NAC can be given well after the 8-10 hour window often described as the “window of opportunity”
- Efficacy may diminish progressively if NAC is administered late after the acetaminophen ingestion; however, the potential benefit far outweighs any theoretical risk.
 - NAC should not be withheld even after very late presentations i.e, > 24 hrs if clinically indicated based upon laboratory findings.

Why do specialists at NJPIES often suggest therapy with NAC despite what appears to be a serum APAP level below the level of toxicity as plotted against time on the Rumack-Matthew nomogram?

- In order to use the nomogram, with a reasonable degree of certainty, the EXACT time of ingestion must be known and the product should be regular release not extended release. However:
 - suicidal patients may not always give or be able to give an accurate history as to the time or extent of ingestion
 - the practitioner may not trust the history given to them by the patient

- For these reasons we treat most suicidal patients that have taken acetaminophen as if we do not know the time of ingestion. However, each patient's data is looked at carefully and a decision based on that information is tailor-made to the individual patient. We attempt to explain our rationale for therapy to the treating physician, however, the final decision is the clinical decision of the treating physician

Does NJPIES still suggest the use of oral NAC as a “short course” regimen 6 doses in place of the traditional oral 17 dose course?

- Traditionally, when one determines that a patient with an acetaminophen overdose requires therapy with NAC, it was administered orally for 17 doses.
- For over ten years NJPIES has been suggesting a shortened course of oral NAC.
 - 140 mg/kg loading dose and 70 mg/kg every 4 hours for a total of 6 doses in 24 hours
 - At the end of the 24 hours we suggest obtaining a repeat APAP level and set of LFTs. If APAP is non detectable and the LFTs are within normal range NAC can be discontinued.

Is greater than 17 doses of oral NAC or 21 hours of IV NAC ever suggested?

- For patients with significant hepatic involvement, signs of persistent liver damage, liver failure and/or encephalopathy at the end of 17 doses, NAC should be continued. It has been suggested that NAC be continued until the INR < 2 (without Vit K administration), transaminases < 1,000 and encephalopathy has cleared.
- We continue the IV NAC at the same dose the patient received during the 16 hour infusion
 - At the end of the 16 hour bag we then suggest repeating LFTs, INR, Creatinine, etc to help make the determination if another dose is needed
- If one elects to treat orally, the 70mg/kg dose every 4 hours is continued for an additional 24 hours and then a reassessment is performed.

What are the specific issues that need to be worked out between pharmacy and nursing with respect to IV administration of NAC?

- IV NAC storage and IV drip preparation and responsibilities must be decided. Delays in preparation will delay administration and potentially result in hepatotoxicity.
- Administration takes place in three consecutive phases with 3 separate IV drips:
 - Loading Dose
 - Second Dose
 - Third Dose
- If made in the pharmacy we suggest the 1st maintenance infusion be sent to the place of administration with the loading dose.
- Every institution will have to decide how they want to handle the “delivery” of the second maintenance infusion. Things that need to be considered include:
 - The second maintenance infusion must be available immediately following the completion of the first maintenance dose. This must be planned with the pharmacy.
 - Loss of the second infusion while transporting the patient from the emergency department to another floor will increase cost and delay of NAC administration.

Is Acetadote approved for both adults and children?

- Yes, it is approved for both adults and children
- The package insert for Acetadote contains a table with adult dosing and another for pediatric dosing
- Dosing in children requires weight based alterations in the volume of fluid the NAC is placed into, potentially the type of fluid used, as well as the amount of NAC given

- The dosing tables in the package insert (copied below) make it easy to choose the proper IV dose to prepare the IV infusions

After IV NAC is started should liver function tests be re-assessed?

- While every case is different, we suggest repeating AST/ALT/ INR at or near the end of the third dose (approximately 21 hours after therapy has begun).
- It is imperative that these levels be ordered STAT and the results evaluated immediately

What will be suggested if the AST/ALT/INR are elevated?

- Because an elevation in these enzymes are a sign of hepatotoxicity, continuation of the IV NAC infusion may be warranted.
- Our staff will make recommendations on further therapy based upon patient specific information.

How does one switch from IV administration to oral administration or oral administration to IV

- There is no “standard” conversion method we tailor each case is handled based upon patient specific factors

Acetadote® Three-Bag Method Dosage Guide by Weight (patients ≥ 40kg)

Body Weight		Loading Dose 150 mg/kg in 200 mL 5% dextrose over 60 minutes	Second Dose 50 mg/kg in 500 mL 5% dextrose over 4 hours	Third Dose 100 mg/kg in 1000 mL 5% dextrose over 16 hours
(kg)	(lb)	Acetadote (mL)	Acetadote (mL)	Acetadote (mL)
100	220	75	25	50
90	198	67.5	22.5	45
80	176	60	20	40
70	154	52.5	17.5	35
60	132	45	15	30
50	110	37.5	12.5	25
40	88	30	10	20

Acetadote® Three-Bag Method Dosage Guide by Weight (patients < 40kg)

Body Weight		Loading Dose 150 mg/kg over 60 minutes		Second Dose 50 mg/kg over 4 hours		Third Dose 100 mg/kg over 16 hours	
(kg)	(lb)	Acetadote (mL)	5% Dextrose (mL)	Acetadote (mL)	5% Dextrose (mL)	Acetadote (mL)	5% Dextrose (mL)
30	66	22.5	100	7.5	250	15	500
25	55	18.75	100	6.25	250	12.5	500
20	44	15	60	5	140	10	280
15	33	11.25	45	3.75	105	7.5	210
10	22	7.5	30	2.5	70	5	140

Cumberland Pharmaceuticals. Acetadote® package insert. Nashville, TN; 2006.

NJPIES RECOMMENDED MEDICATION LIST FOR EMERGENCY ROOMS

NJPIES Suggested Antidote list 9/06

GENERIC NAME	INDICATION	DOSAGE FORM	DOSE	APPROXIMATE TOTAL DOSE NEEDED FOR A 70KG PATIENT	APPROXIMATE AMOUNT TO TREAT ONE 70KG PATIENT	EXTRA NOTES
Acetylcysteine Oral (NAC, Mucomyst)	Prevention/Treatment of Acetaminophen toxicity	20% (20g/100mL) 30 mL vials 10% (10g/100ml) 30 ml vials	Current Dosing Scheme: Loading: 140 mg/kg Maintenance: 70 mg/kg x 6 doses FDA dosing scheme: 70 mg/kg x 17 doses	Current: LD: 9800mg MD: 29400mg FDA: 83300mg	Current: 2 vials (20%) 17 doses: 5 vials (20%)	Check LFTs after 6 doses and APAP level. IF APAP level undetected and if LFTs normal, do not need to continue onto 17 doses.
Acetylcysteine IV (Acetadote)	Prevention/Treatment of Acetaminophen toxicity	20% (20g/100mL) 30 mL vials	One Full Dose = 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, and then 100 mg/kg over 16 hours	21,000mg	4 vials	Package Insert/NJPIES has dosing table available according to patients weight and appropriate dilution
Activated Charcoal with/without Sorbitol	Single or Multiple doses to bind to agents in overdoses	Various sizes some contain sorbitol 50g/240 ml (common size)	Initial (with sorbitol): 50-100g or 1g/kg (wt-based) Repeat Dose (without sorbitol): 25g or 0.5g/kg (wt-based) every 2-4 hours	Initial (wt-based): 70g Repeat (wt-based): 35g every 2-4 hours	Initial: 2 bottles Repeat: 1 bottle	No longer routinely administered Consider when: the toxin is likely to be adsorbed to charcoal large quantities of the toxic substance may be available for absorption
Atropine Sulfate	Organophosphate and Carbamate insecticides	IV: 1mg/mL vial	IV: 2-5mg, repeat every 5-60 min until see effect		IV: 2-5 mg initially then as needed (max 6 vials)	There is no max dose for treating exposures to these chemicals. Doses are titrated to response.

CALCIUM DISODIUM EDETATE (EDTA)	LEAD TOXICITY	200MG/ML IN 5 ML AMPULES	50-70 MG/KG/D DEEP IM (PREFERRED) OR SLOW IV INFUSION IN 3-6 DIVIDED DOSES UP TO 5 DAYS	3500MG-4900MG	4 - 5 AMPULES	DO NOT SUBSTITUTE WITH SODIUM EDTA BECAUSE OF THE RISK OF HYPOCALCEMIA
Calcium gluconate Calcium Chloride	Hypocalcemia, Calcium Antagonist Toxicity, Hydrofluoric Acid Exposure	Various sizes Topical: extemporaneously prepared	calcium channel blocker OD 3g calcium gluconate (30ml 10%) 1g calcium chloride (10 ml 10%) Topical (HF): 2.5% gel to affected area every 4-6 hours until pain resides usually in 3-4 days		Dependent upon size stocked	These are starting doses and much more may be required
Cyanide Antidote Kit	Cyanide Poisoning	1 Kit contains: 2 ampules of sodium nitrite, 2 ampules of sodium thiosulfate, and 12 pearls of amyl nitrite	Break ampule of Amyl nitrite and have victim inhale for 30 seconds every min. Use a new ampule every 3 min. Then Sodium nitrite 300mg inj. At 2.5-5mL/min Then inject a slow IV 12.5g of 25% Sodium thiosulfate		1 Kit	
Deferoxamine	Iron Toxicity	500mg in 5mL vials	IM: 10mg/kg up to 1 g every 8 hours IV: 10-15mg/kg/h (do not exceed 6g in 24 hours)	IM: 700mg IV: 1050mg/h	IM: 2 vials per dose IV: 3 vials per dose	

DIGOXIN FAB FRAGMENTS	DIGOXIN TOXICITY	DIGIBIND - 38MG/VIAL DIGIFAB – 40MG/VIAL (EACH VIAL WILL BIND ABOUT 0.5MG OF DIGOXIN)	DOSE BASED UPON DIGOXIN LEVEL OR APPROXIMATE QUANTITY IF KNOWN IF UNKNOWN AMT (ACUTE TOX): 20 VIALS		NEED TO STOCK AT LEAST 20 VIALS	FOR EXACT DOSING, CONTACT NJPIES
Dimercaprol(BAL)	Arsenic, lead, mercury,	100mg/mL in 3 mL ampules	3-5mg/kg deep IM every 4hr for 2 days , then 3-5mg/kg every 4-12hr for up to 7 additional days	2520-4200mg(2 days) 2940-14700mg(7 days)	9-14 amps (2 days) 10-49amps(7 days)	Arsenic , Lead, and Mercury limit to 5 days
Diphenhydramine	Extrapyramidal drug reactions or allergic reactions	10mg/ml 50mg/ml injection solution Various sizes	Given IV or IM 10-50mg every 2-3hrs as needed	50 mg/dose	2-3 doses	Max parenteral dose 400mg/day
Epinephrine	Management of anaphylaxis reactions or cardiac arrest	0.1mg/mL[1:10,000] (10mL) injection solution 1mg/mL[1:1000](1mL)	Anaphylaxis: 0.3-0.5 ml IM or SC		Enough to administer at least 5 doses per patient	
Ethanol	Ethylene glycol or methanol toxicity or ingestion	10% in D5W	Loading – 8 mL/kg Maintenance – 0.83mL/kg/hr	Loading – 532mL Maintenance – 58.1mL/hr * 24 hr=1394.4mL	1926.4 mL total	Not needed if Fomepizole is stocked. Fomepizole is preferred
Flumazenil	Benzodiazepine	0.1mg/mL 5 and 10 mL vials	0.2mg IV (2mL) wait 3 minutes for a response 0.3mg IV (3mL) wait 3 minutes for a response 0.5mg IV (5mL) given at 60 second intervals up to a cumulative dose of 3mg	1mg	One 10mL vial	Do not use in : patients chronically using, or “dependent” upon benzodiazepines, or in those that may have taken a medication that can cause seizures

FOMEPIZOLE	ETHYLENE GLYCOL , METHANOL	1G/ML 1.5ML VIAL	15MG/KG IV FOLLOWED BY 10MG/KG IV EVERY 12HRS THEREAFTER (5 DOSES TOTAL)	3850 MG	4 VIALS IN CASE OF A LARGER PATIENT	
Glucagon	Beta adrenergic antagonists (Propranolol), Calcium channel blockers, Hypoglycemic agents	Powder for injection 1 mg vial (1mg equals one unit) *Do not reconstitute with propylene glycol, diluent which may be provided with product*	Hypoglycemia: 1mg IM may repeat in 20minutes as needed Beta-blocker/calcium channel blocker OD: 5-10mgIV over 1 minute followed by an infusion of 1-10mg/hr	1mg or 1- 10mg/hr(will vary depending on patient)	10 vials	Amount needed will vary depending on patient Consider octreotide for a sulfonylurea overdose Associated with a high risk of vomiting, use caution in the obtunded patient
METHYLENE BLUE	Methemoglobinemia	1%(10MG/ML) 1ML, 10ML AMP	initial dose 1-2mg/kg iv	70-140mg (7-14ml)	two 10ml amps	
Naloxone	Opiates	0.4mg/mL 1mL, 10mL	0.4-2mg IV every 2-3 minutes as needed May need to repeat doses every 20-60 minutes	Usually 0.4-2mg but will vary with each patient	Up to 3 10ml amps	-If no response is observed after 4mg , question the diagnosis -In patients who are opioid dependent , use 0.1-0.2mg increments to avoid too rapid withdrawal
Octreotide	Oral hypoglycemics	Injection solution as acetate 0.05mg/mL(1mL) 0.1mg/mL(1mL) 0.2mg/mL(5mL) 0.5mg/mL(1mL) 1mg/mL(5mL)	50-100 mcg SQ or IV every 6-12 hrs in a 24 hr period	100mcg-200mcg	2* 0.2mg/ml (5mL)	Patient must be monitored for hypoglycemia after octreotide has been administered. For patient specific recommendations contact NJPIES.

PHYSOSTIGMIN E	ANTICHOLINERGICS , ANTIHISTAMINES, ATROPINE, SCOPOLAMINE, INTRATHECAL BACLOFEN, SOME PLANTS, MUSHROOMS	1MG/ML 2ML AMP	0.5-2MG IV/SUBQ/IM TO START AND MAY BE REPEATED EVERY 20MINUTES UNTIL A RESPONSE OCCURS OR TOXICITY DEVELOPS	2MG BUT WILL VARY WITH EACH PATIENT	1 AMP OR GREATER	CAUTION, MAY PRODUCE SERIOUS SIDE EFFECTS. ADMINISTER VERY SLOWLY. DO NOT USE IF QRS > 100 MS
Phytonadione(vitamin K)	Drug or anticoagulant induced vitamin K deficiency	2mg/mL (5mL) 10mg/mL (1 mL) 5mg/tablet (Mephyton)	1-10mg IV/PO, may repeat every 12 hours	2.5-10mg depending on degree of INR elevation	One vial of 5mL One bottle (100tabs)	IV administration should not exceed 1mg/min
Polyethylene glycol (PEG) (GoLyteLy,Colyte)	Used for whole bowel irrigation. Help remove what may be in the gut	Powder for oral solution (4000mL)	1.5-2L/hr until rectal effluent is clear	4L	One 4L bottle	To be effective, must be administered rapidly!
Pyridoxine(vitamin B6)	Isoniazid)	100mg/mL 10 and 30mL vials	- Acute Isoniazid intoxication: dose equal to amount of Isoniazid ingestion - 5 grams if amount taken is not known	Depends upon what drug has been ingested	Depends upon what drug has been ingested	
Pralidoxime(2-PAM, Protopam)	Acetylcholinesterase inhibitors (Organic Phosphorus,pesticides, insecticides, tacrine, carbamate)	600mg/2mL Injection powder for solution: 1gram	1-2g at 0.5g/min or infused in 100mL NS over 15-30min Continuous infusions of 500 mg/hr may be needed in severe poisonings	12g may be needed over a 24 hour period		
crotalidae polyvalent immune fab (OVINE) CroFab	Rattlesnake and copperhead envenomations	4-6 vials to start	4-6 vials to start	Up to 18 vials may be needed for severe envenomations	4-6 vials to start	

Section C

New Jersey Poison Information and Education Fact Sheet

Suggested file section: "C" Calcium Gel

Overview

Calcium Gluconate Gel

Calcium Gluconate (or calcium carbonate gels an alternative) is used for the management of hydrofluoric (HF) burns. HF is an inorganic acid that readily penetrates the skin and binds to calcium causing deep tissue layer destruction and burns. Severity and rapidity of onset of signs and symptoms depends on the concentration, duration of exposure, and penetrability of the exposed tissue. Hydrofluoric acid burns are very painful. After flushing the exposed skin with water calcium gel may help alleviate the pain and prevent extension of the burn. Higher concentrations and further management will vary depending upon the patient's condition (i.e., severity, systemic symptoms, etc.)

The calcium containing gels can be made as follows:

Calcium Gluconate

Combine 3.5 g of calcium gluconate with 150 ml of a water-soluble lubricant (K-Y Jelly)

Calcium carbonate

Triturate ten 650 mg tablets into a fine powder

Add 20 ml of a water-soluble lubricant (K-Y Jelly)

A commercial calcium gluconate gel is available from Pharmascience in Buffalo, NY (800 207-4477) \$27.55 tube 6 tube minimum with a 5% shipping and handling charge added.

New Jersey Poison Information and Education Fact Sheet

Suggested file section: “C” cyanide

Overview

Cyanide is a potentially lethal chemical found in many NJ facilities. Cyanide is used in electroplating, metal refining, photography and other industrial processes. In addition, cyanide can be liberated during fires in closed spaces involving common materials such as silk, polyurethane, synthetic rubber, etc. A large proportion of individuals dying at the scene of a fire will die with an elevated blood cyanide level. Cyanide poisoning has been reported from the accidental or intentional ingestion of acetonitrile based artificial nail glue solvent or removers. Cyanide is formed from acetonitrile through metabolism via the P450 system and then released by catalase. Cyanide is listed as a possible war gas, classified as a “blood agent,” by the World Health Organization.

Cyanide Toxicity

Cyanide can reach the systemic circulation via the oral, dermal, gastrointestinal and pulmonary routes. Once absorbed, cyanide interferes with many cellular enzymes including cytochrome oxidase. Interference with cytochrome oxidase causes a disruption in aerobic energy production, resulting in cellular hypoxia, anerobic respiration and profound acidemia despite adequate oxygen availability. In-fact, lactic-acidosis (level greater than 10 mm/L) with no other explanation combined with a clinical scenario consistent with cyanide exposure is considered diagnostic. Clinical manifestations of cyanide toxicity is dependent upon the type of cyanide involved, route of exposure as well as underlying medical conditions. Symptoms usually begin within minutes of exposure to inorganic and gaseous forms. CNS symptoms resemble that of progressive hypoxia.

Headache	Lethargy	Anxiety
Confusion	Convulsions	Coma

Cardiac effects include an initial period of bradycardia and hypotension followed by reflex tachycardia and hypertension. This period is followed by bradycardia and hypotension. Non-cardiogenic pulmonary edema has been reported in acute overdoses while cardiogenic pulmonary edema has been reported in the case of chronic exposure.

It has often been stated that dermatologic manifestations of cyanide include “cherry red skin”. This color change may be related to decreased tissue utilization of oxygen and resultant increased venous hemoglobin oxygen saturation. Following the same mechanism, retinal veins often appear similar in color to retinal arteries.

Following ingestion of cyanide, abdominal pain, nausea and vomiting can also be expected.

Laboratory findings include a wide anion gap metabolic acidosis, elevated lactate (above 10 mmol/L), and a venous oxygen saturation > 90% (pO₂ >50 mmHg). These findings are not specific for cyanide (similar findings can be seen after exposure to other toxic agents including hydrogen sulfide) and diagnosis is based upon presence of these laboratory abnormalities, clinical findings and a high index of suspicion. The presence of cyanide can be confirmed in blood; however, at this time determination of blood cyanide concentrations would take too long to be of clinical utility.

Management

Elimination of cyanide is primarily via conversion to thiocyanate and then elimination of thiocyanate via the kidneys. The conversion of thiocyanate requires the enzyme rhodanase along with endogenous sulfur. In the acute exposure, inadequate endogenous sulfur stores results in a decreased detoxification process.

As in all critically ill patients, oxygen is always administered and good supportive care is mandatory. Attempt to correct the metabolic acidosis should be aggressive. The treatment of cyanide poisoning in the United States has remained consistent over nearly 100 years despite much dispute regarding the mechanisms and degree of efficacy. The cyanide kit (also known as the “Lilly Cyanide Kit”) is the standard antidote kit available in hospitals and at risk areas in the United States. This kit contains crushable ampules of amyl nitrite, injectable sodium nitrite and sodium thiosulfate. Thiosulfate acts as a sulfur donor, allowing the enzyme rhodanase to convert cyanide to thiocyanate, a non-toxic stable compound. The mechanism of nitrites and their role in the management of cyanide toxicity is less clear. It has been postulated that beneficial effect of nitrites come from their ability to convert hemoglobin to methemoglobin. Cyanide has a greater affinity for methemoglobin than cytochrome oxidase. Binding of cyanide to methemoglobin rather than cytochrome oxidase, allows for the cytochrome oxidase to participate in aerobic metabolism (as normal). The effectiveness of sodium nitrite appears to occur far before the development of significant methemoglobinemia. There is thought that the effect of the nitrite is to produce vasodilatation.. Nitrites may have other beneficial effects including increasing hepatic blood flow.

Sodium thiosulfate is administered IV as a 25% solution; 12.5 grams in the adult and 1.65 ml/kg in the child. Once carbon monoxide poisoning has been eliminated in the case of a closed space fire, sodium nitrite 3% is given IV over 2-4 min 300 mg in the adult and based upon a child’s hemoglobin (chart available upon request). Amyl nitrite pearls are suggested when IV administration will be delayed. The glass ampules are crushed and the person should be allowed to inhale the amyl nitrite for 30 sec on and off in a cyclical fashion until an IV line has been established and sodium thiosulfate/sodium nitrite has been administered.

Other agents not commercially available but often discussed at this time include hydroxycobalamin (precursor of vitamin B₁₂). Hydroxycobalamin acts as a chelator, binding to cyanide. This results in the formation of cyanocobalamin (vitamin b12) which is eliminated via the kidneys.

Conclusion

With cyanide toxicity being of rapid onset, having non-specific clinical features, and less than rapid blood assay capabilities to confirm cyanide’s presence, therapy must be empiric based upon a high index of suspicion. The clinical picture of rapid loss of consciousness or seizures with a persistent, severe wide anion gap metabolic acidosis and venous hyperoxia should alert the clinician to the possibility of cyanide poisoning. Therapy **SHOULD NOT BE DELAYED!**

Based upon the current state of terrorism-readiness, it is imperative that cyanide antidote kits, and at minimum sodium thiosulfate, be readily available for use, with the staff fully trained to administer it.

Section

I

New Jersey Poison Information and Education Fact Sheet

Suggested file section: "I" INH

Overview

When ingested by itself, INH is rapidly absorbed from the GI tract with peak levels occurring within 1-2 hours of ingestion. Once absorbed, INH distributes very well throughout the body, including the central nervous system. INH is then metabolized in the liver via acetylation and hydrolysis.

One consequence of chronic INH use is neurotoxicity, which is manifested as a peripheral neuropathy. This peripheral neuropathy can be prevented by the concurrent administration of pyridoxine (vitamin B6). **In the acute overdose situation neurotoxicity is manifested as SEIZURES.**

It is postulated that INH induced seizures are caused by a decrease in the production of GABA (an inhibitory neurotransmitter) which results from INH's effect on pyridoxine. INH adversely affects pyridoxine in several ways.

It appears that INH interferes with the enzymes needed to produce the active forms of pyridoxine. It is the active form of pyridoxine that is used in the production of GABA. In addition, INH combines with pyridoxine to enhance the renal elimination of pyridoxine, further decreasing the availability of pyridoxine which is needed for GABA production.

Seizures caused by an overdose of INH usually occur within two hours of ingestion (but have been reported up to 6 hours later). INH induced seizures are generally tonic-clonic and **resistant** to conventional anticonvulsants.

While the exact amount of INH necessary to cause seizures is variable, seizures are not uncommon when acute ingestions approach 20mg/kg (less if the patient has an underlying seizure history). Management of seizures includes the use of a benzodiazepine IV and pyridoxine.

Use of Pyridoxine

Patients actively seizing or in coma should be given 1 gram of pyridoxine for each gram of INH ingested (maximum dose is 5 grams). If the exact amount is not known an adult patient should be given the full 5 grams, a child can be given 70 mg/kg up to 5 grams. Pyridoxine should be given IV at a rate of 1 gram over 2-3 min. If the patient stops seizing before the total dose is given, the remainder should be placed into 500 ml of D5W for administration over 4-6 hours. The dose can be repeated if seizures reoccur or if mental status remains depressed. Since the bioavailability of pyridoxine is so good, if injectable pyridoxine is unavailable, and the patient is not vomiting, tablets of pyridoxine may be crushed and put down an NG tube.

Section L

To: Directors of Pharmacy, Medicine, Emergency Medicine, Anesthesiology,
Critical Care, Pediatrics and VPs Nursing
From: Bruce Ruck, Pharm.D.
Date: 6/25/07
Re: lipid emulsion as an antidote

The administration of lipid emulsion as an antidote is a modality that health care professionals may see more of in the future. Current research is pointing to a probable role of lipid emulsion rescue in refractory cardiotoxicity from local anesthetics and tricyclic antidepressants and possibly other sodium channel blocking agents. Some toxicologists and anesthesiologists are now suggesting lipid emulsion be available to be used as an antidote wherever local anesthetics are administered as well as in the ED for life-threatening local anesthetic and tricyclic antidepressant overdoses.

While we are sending copies of this to other health care professionals in your institution, please check our distribution list and forward this document to others you deem appropriate. Please let me know if we can be of assistance with this or any medication related question. Just a reminder, Drug & Poison information calls should be directed to 800-222-1222, administrative matters to 973-972-9280

A feared and deadly complication of local anesthetic use is cardiac toxicity for which antidotal therapy has traditionally not been available. Systemic toxicity of local anesthetics can occur from an overdose, decreased drug metabolism, or more commonly an inadvertent intravascular injection intended for another route. At high serum levels, decreased myocardial contractility combined with vasodilation has been well reported in the literature. Cardiovascular collapse secondary to these anesthetics is often refractory to standard advanced cardiac life support and pharmacologic interventions.

Literature on the use of lipid emulsion as an antidote for local anesthetic toxicity started appearing in 2006. Dr. Guy Weinberg demonstrated that rats administered lipid infusions tolerated higher doses of bupivacaine than did rats not receiving lipids. This beneficial effect in rats receiving bupivacaine led to a lipid rescue trial in dogs. Canines were given 10 mg/kg of bupivacaine to induce cardiac toxicity. This was followed by a saline infusion or a 4ml/kg (20% lipid) bolus followed by a continuous infusion of lipids (0.5 ml/kg/min for 10 minutes). Dogs receiving lipids recovered cardiac function within minutes and all survived; while none of the dogs receiving the saline infusion survived.

Rosenblatt describes the successful use of lipids in reversing Bupivacaine associated cardiac arrest. A 58 yr-old patient undergoing arthroscopic surgery was given 20 ml of bupivacaine 0.5% and 20 ml of mepivacaine 1.5%. Approximately 30 seconds after administration of local anesthetic, the patient seized and recovered with propofol. Another seizure occurred approximately 90 seconds later and an asystolic cardiac arrest occurred. Advanced cardiac life support was performed with little response. 100 ml of 20% Intralipid® (lipid emulsion) was given. Within 15 seconds of lipid bolus, a sinus rhythm returned at 90 beats/min. A lipid infusion of 0.5 ml/kg/min for 2 hours was administered.

The exact reason why lipids are beneficial is not known. One potential mechanism is that the lipophilic anesthetic is attracted to and drawn into the lipid emulsion in the plasma from tissue and organs (such as the myocardium). The movement of the anesthetic causes a shift of the anesthetic from the site where it exerts its toxic effect into the lipid layer of the fat emulsion.

Currently no human clinical trials have been completed using lipids as an antidote in the management of local anesthetic toxicity. Available data consists of anecdotal (none published) reports and a published case report by Rosenblatt.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are another class of agents with significant morbidity and mortality in the OD situation. Similar to local anesthetics, TCAs are lipophilic drugs that have sodium channel blocking effects. TCA overdoses are associated with decreased cardiac output, arrhythmias, and seizures. Along with decreased cardiac output, TCAs block alpha-adrenergic receptors decreasing peripheral vascular tone resulting in hypotension. Like the local anesthetics, it is thought that lipid emulsions can attract TCAs into the plasma and out of tissues where their toxic effects occur. Similar to the local anesthetics, human and animal data using lipids as an antidote is limited.

Recommendations:

Based upon the limited data (human, animal and anecdotal), the following has been suggested by the toxicologists at NJPIES and/or other poison centers for local anesthetic overdoses and overdoses caused by TCAs **that do not respond** to more conventional therapy.

Suggestion 1

1. IV bolus of 20% lipid emulsion at 1 ml/kg over 1 minute every 3-5 minutes, repeat up to 3 times
2. continue chest compressions
3. after 3 boluses or signs of recovery, switch to continuous infusion of 0.25 ml/kg/min until hemodynamically stable
4. no dose limit, but 8 ml/kg will probably not have any extra benefit
5. Dr. Weinberg also does NOT recommend the use of propofol in this situation

Suggestion 2 (resuscitating an adult weighing 70kg)

- 1) Take a 500ml bag of Intralipid 20% and a 50ml syringe.
- 2) Draw up 50ml and give stat IV, repeat twice
- 3) Then attach the Intralipid bag to an IV administration set (macro drip) and run it IV over the next 25 minutes.
- 4) Repeat the initial bolus up to twice more – if spontaneous circulation has not returned.

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- Personal communication with: Gary Zaloga, Baxter

Section M

Overview

To allow for oxygen transport in the red blood cell iron in the hemoglobin molecule must be in the ferrous (Fe^{2+}) state to properly carry and release oxygen. When oxidation (ie, loss of an electron) of the iron moiety occurs, ferrous iron (Fe^{2+}) is converted to the ferric (Fe^{3+}) state producing methemoglobin.

Because of changes in the stoichiometric configuration, Ferric heme (Fe^{3+}), is not capable of binding oxygen. In addition, any oxygen bound is less able to be released and thus available to the tissues. With decreased oxygen binding and decreased release the patient becomes “hypoxic”.

While the body is continually exposed to oxidative stress that converts ferrous iron (Fe^{2+}) to the ferric (Fe^{3+}) state, several enzymatic pathways exist to keep the methemoglobin percentage at a level which does not produce any clinical problems, usually less than 1-2%. These pathways convert methemoglobin back to functional hemoglobin.

Methemoglobinemia occurs when exposure to a medication or chemical increases the rate of methemoglobin production to rise to a level that exceeds the bodies’ ability to convert it back to hemoglobin. Medications and chemicals reported to cause this reaction include:)

Topical anesthetics (Benzocaine, Lidocaine)
Sulfonamides
Dapsone

Nitrates/nitrites (including: NTG, nitroprusside)
Pyridium,
Aniline compounds found in inks, polishes, paints & varnishes

The clinical significance of methemoglobinemia depends upon the percentage of methemoglobin. At 1-< 3% no symptoms are expected. As the percentage rises the patient develops gray skin discoloration, cyanosis, shortness of breath, headache, fatigue, acidosis, dysarrhythmias, seizures and ultimately, at high levels above 50%, death may occur.

Methylene blue is the antidote of choice for drug/chemical induced methemoglobinemia, in non-G6PD-deficient patients. When given at the recommended dose it rapidly (within minutes) leads to the conversion of hemoglobin from methemoglobin.

Methylene blue

Methylene blue is effective in the management of drug/chemical induced methemoglobinemia because it ultimately enhances the conversion of methemoglobin to hemoglobin. Methylene blue gains an electron (i.e., is reduced) in the presence of NADPH and diaphorase II and becomes converted to leukomethylene blue. Leukomethylene blue then reduces the iron moiety (Fe^{3+}) to (Fe^{2+}); and thus methemoglobin becomes re-converted to hemoglobin.

The usual suggested dose of Methylene Blue is 1-2 mg/kg IV over 5 min. Repeat doses in 1hr may be necessary if significant methemoglobinemia continues.

Summary

Methylene blue is an important antidote that should be available in the emergency department and hospital pharmacy for the management of methemoglobinemia

Letter submitted for publication

Dear Sir:

As a result of a recent report by the Food and Drug Administration (FDA) several local hospitals in New Jersey reported to the New Jersey Poison Information and Education System (NJPIES) that they have removed methylene blue from their hospital formularies. The report, a Public Health Advisory, includes 20 cases of adverse events that are temporally but not causally associated with the use of blue dye in enteral feeding formulas.¹ The report provides background information that while the dye FD&C Blue No. 1 (Blue 1) can be a mitochondrial toxin, toxicity has only been reported in association with use in enteral feeding, even though the utility of this procedure is not supported in the literature.^{2,3,4} The report also mentions that methylene blue may have even greater toxicity than Blue 1.

We recommend against the removal of methylene blue from hospital formularies since methylene blue remains the only antidotal treatment of methemoglobinemia. Methemoglobinemia is an oxidized state of hemoglobin that may result from infectious as well as toxic causes and impairs oxygen delivery to tissue. While methemoglobin spontaneously reverts to hemoglobin at a rate of about 15% per hour, methylene blue is used to treat the more severely ill patients. Methylene blue increases reversion to hemoglobin by facilitating NADPH-Methemoglobin reductase where increased generation of leukomethylene blue restores methemoglobin to normal hemoglobin.^{5,6} Even though there may be complications, such as treating those with G6PD deficiency, methylene blue is considered a safe drug for this use.

Current recommendations concerning the stocking of methylene blue in emergency departments advise a minimum of ten 10 mL vials of methylene blue so that emergency staff are adequately prepared for any methemoglobin cases that may arise.⁷ While the FDA advisory takes note of how poorly understood the adverse reactions are to the use of Blue 1, we feel that including methylene blue in their report has perhaps led to a misunderstanding and the removal of a genuinely safe and useful drug from hospital formularies. We recommend that hospitals maintain methylene blue in adequate quantities for the treatment of patients who are diagnosed with symptomatic methemoglobinemia.

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New Jersey Poison Information and Education System

Section O

New Jersey Poison Information and Education Fact Sheet

Suggested file section: "O" octreotide

Overview

Sulfonylureas are a commonly prescribed class of medication for the management of diabetes. It is not uncommon to find that a medication from this class has accidentally been ingested by a toddler or taken intentionally by an adolescent or adult. Sulfonylureas lower glucose by facilitating the release of insulin from the beta islet cells of the pancreas. In an overdose, hypoglycemia can occur and may be prolonged. Initial symptoms of mild hypoglycemia include, fatigue, tachycardia, dizziness, diaphoresis and agitation. As hypoglycemia progresses, metabolic acidosis, seizures, cardiovascular collapse and death can occur. Onset and duration of hypoglycemia is related to an individual agent's pharmacokinetic profile as well as an individual's renal and hepatic function.

Sulfonylurea induced hypoglycemia is often managed with the administration of IV dextrose. Boluses of D50W plus infusions of D10W are commonly administered. Unfortunately, administering concentrated dextrose solutions often results in a "yo-yo" effect. Glucose rises, rapidly producing hyperglycemia (in the 200-400 mg/dl range). Because sulfonylureas stimulate insulin release, hyperglycemia from the administration of glucose is followed within approximately an hour by severe hypoglycemia (20-50 mg/dl range), which can be prolonged. This hypo-hyperglycemic cycle is not uncommon and continues until the boluses of dextrose are stopped. In addition to the administration of dextrose, some have advocated the use of glucagon to raise the glucose in the face of a sulfonylurea overdose. Glucagon works by converting glycogen stores to glucose, as with glucose infusions, many patients will develop the hyperglycemia-hypoglycemia cycling as noted above. Initial subcutaneous or intramuscular injections of 1 mg in adults, 0.5 mg in children may be followed by a continuous infusion of 1 to 5 mg/hour. However, when using a continuous infusion the diluent that is supplied with the glucagon should not be used because of the phenol contained in it. To prevent phenol toxicity glucagon can be reconstituted with 10 ml of 5% dextrose in water or normal saline. Many people develop nausea and vomiting after the administration of glucagons, limiting our ability to feed a patient. Ingestion of food is strongly encouraged after an overdose of a sulfonylurea. To avoid the hyper-hypoglycemic cycling we have been recommending the use of octreotide for managing hypoglycemia associated with an overdose of a sulfonylurea.

Octreotide

Octreotide, a somatostatin analogue is thought to bind to a somatostatin receptor located in pancreatic beta islet cells. Binding of octreotide to these receptors causes a decrease in calcium influx, followed by a decrease in insulin secretion; in theory, almost a "perfect" antidote for sulfonylureas. For the management of hypoglycemia associated with an overdose of a sulfonylurea, octreotide has been administered at a dose of 50 mcg to 100 mcg subcutaneously. Because the pharmacologic effect of sulfonylureas in the overdose situation may surpass octreotide's duration of action, repeat doses of octreotide every 6-12 hours may be necessary. We suggest feeding the patient and not making them NPO whenever possible. The extent and duration of hypoglycemia is not predictable and based upon many factors, including the specific agent and dose ingested, concomitant medications taken and underlying medical problems. Because duration and degree of hypoglycemia is not predictable we urge frequent blood glucose readings (every 30-60 min. or more frequent if necessary), and monitoring of glucose for at least 24 hours post ingestion, longer if hypoglycemia is prolonged or frequently recurring.

Because octreotide has proven beneficial, we suggest either stocking octreotide in the emergency department or making sure it is readily available if needed.

Section

S



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To: Directors of Pharmacy
cc. Directors of Medicine, Emergency Medicine, Cardiology, Psychiatry, Chair P&T committee,
VPs Nursing & Medical Affairs
From: Bruce Ruck, Pharm.D.
Re: Poison Information Update:
Date: 7/03

Attached you will find the latest information to be added to the NJPIES Poison Management binder which was sent to all Directors of Pharmacy in April 2002. This update contains information on the monitoring of patients with a suspected ingestion of **Celexa (citalopram) or Lexpro (escitalopram)**. Unlike other Serotonin reuptake inhibitors, we are currently suggesting that patients suspected of having ingested citalopram or escitalopram receive ECG monitoring for at least 24 hrs (longer if clinically appropriate), with QTc measurements being done every 2 hrs (or more frequent if clinically indicated).

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Please let me know if we can be of assistance with this or any medication related question. Just a reminder, Drug & Poison information calls should be directed to 800 222-1222, administrative matters to 973 972-9280.

New Jersey Poison Information and Education Fact Sheet

Suggested file section: "S"

Overview

Selective Serotonin Reuptake Inhibitors (SSRIs) have become the most widely prescribed class of antidepressants. While SSRIs have been considered relatively less problematic in the overdose situation than tricyclic antidepressants (TCAs) they are not devoid of potential problems. Until recently, not much difference has been noted in the clinical manifestations between an overdose of one SSRI or another SSRI. As such our management and monitoring parameters have been consistent no matter which SSRI was ingested.

However, a recent case report (not yet published) along with a review of published data lead us to alter our monitoring parameters for suspected ingestions of Celexa (**Citalopram**) and Lexpro (**Escitalopram**).

Citalopram & Escitalopram: Need for at least 24 hours of ECG monitoring

NJPIES, along with other poison centers, are now recommending at least 24 hours of continuous ECG monitoring in anyone suspected of ingesting an overdose of **Citalopram or Escitalopram**. During the 24 hours of ECG monitoring we are focusing our attention on the QTc and the QRS interval. We suggest that these intervals be calculated at least every 2 hours (more frequent if prolongation is noted).

At a recent toxicology conference, there was a presentation regarding a patient that developed significant QT prolongation ~ 24 hours after presenting to the hospital with an overdose of citalopram. This patient was not on continuous cardiac monitor at the time symptoms developed, so it was not known exactly when the QT prolongation began, the conduction defect only becoming apparent when the patient collapsed in torsades! In addition, to this case, there are case reports in the literature associating an overdose of citalopram to the development of prolonged QT and QRS intervals.

The mechanism for cardiac conduction abnormalities with citalopram is not well defined. One hypothesis focuses on the citalopram metabolite didemthethylcitalopram (DDCT). Animal studies performed in beagle dogs demonstrated QTc prolongation with fatal arrhythmias when high doses were administered. Fortunately, because of metabolic differences between dogs and humans, the concentration of DDCT in humans is much less than in dogs. However, in the overdose situation the amount of DDCT present may be in high enough concentrations to be problematic.

With respect to escitalopram, there is even a greater paucity of data available in the overdose situation. Escitalopram is the S-isomer of racemic citalopram (in the literature escitalopram is often called S-citalopram). The enantiomer escitalopram appears to be the active moiety of racemic citalopram. It has been estimated that escitalopram is 100 times more active in causing serotonin reuptake inhibition than citalopram.

Like citalopram, escitalopram is also metabolized to a DDCT metabolite known as S-DDCT (representing a single isomer). If in fact it is proven that DDCT is the cause of cardiac conduction abnormalities, one would expect to see similarities between escitalopram and citalopram in the overdose situation.

Summary

The mechanism of action, dose response curve and time to onset for the cardiac conduction abnormalities is not well described after an overdose of these two medications. We believe it is prudent to monitor the ECG for at least 24 hours after presentation to the emergency department until we learn more about potentially life threatening cardiac rhythms associated with these two medications.

