Other Antidotes

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Other Antidotes: Objectives

• Identify the drugs used as chelators and those in the cyanide antidote kit
• Understand the basic concepts of dosing chelators
• Know the side effects associated with the chelators and the cyanide antidote kit
• Know the aspects of laboratory monitoring and their relationship to drug treatment for arsenic, lead and cyanide exposures
• Know the goal of treatment with nitrates when treating for cyanide

Other Antidotes

• Chelators
  – BAL
  – EDTA
  – Penicillamine
  – DMSA
• Heavy Metal Poisoning
  – Arsenic
  – Lead
• Cyanide antidote kit
  – Cyanide Poisoning

Chelators

• The principle is to form a less toxic compound which can be eliminated
• Effectiveness is dependent upon the relative affinity for the toxic metal as opposed to essential metals in the body

Chelators, Cont.

• Desirable characteristics:
  – Soluble in aqueous solutions
  – Able to penetrate sites of metal’s action and storage
  – Resistant to metabolic degradation
  – Functions at physiologic pH
  – Complex less toxic than the uncomplexed metal alone
  – Low affinity for essential metals
  – Greater affinity for the metal than that possessed by the body ligand

Dimercaprol (British Anti-lewisite; Bal)

\[ \text{CH}_2 \quad \text{CH} \quad \text{CH}_2\text{OH} \]

\[ \begin{array}{c|c|c}
\text{SH} & \text{SH} & \\
\end{array} \]
Dimercaprol (British Anti-Lewisite; BAL) continued

- Uses: lead, mercury, arsenic, gold, others
- Penetrates into cells
- Many side effects are dose-related
  - Lacrimation, blepharospasm, paraesthesias, burning sensation on lips, mouth and penis, constriction in the throat and chest, abdominal pain, sweating, painful sterile abscesses, hypertension, tachycardia, and rashes
- BAL is potentially nephrotoxic

Calcium Disodium Ethylenediaminetetraacetate (CaNa₂EDTA; Versenate) continued

- Side Effects: ATN, mucocutaneous lesions with long courses, hypercalcemia, hypokalemia, trace metal deficiency (Zn, Fe, Cu, Mn, Mg), Excessive Chelation Syndrome
- Administer 50-75 mg/kg/d IM or IV in divided doses x 5 days, then re-evaluate
- “EDTA Challenge Test”—lead mobilization test used to determine past significant exposure to lead

D-Penicillamine (Cupramine), Cont.

- Uses: Cu (Wilson’s disease), Hg, As, Pb, Bi, rheumatoid arthritis
- Short term use as chelating agent is relatively safe, use over longer periods is associated with significant side effects: urticaria, lupus erythematosus (N&V common: 10-30% dose related), leukopenia, aplastic anemia, etc.
- Use 250 QID x 5 days for Pb, acutely or As, chronically
Dimercaptosuccinic Acid (Succimer)

**H**  **H**  
**HOOC—C—C—COOH**  
**SH  SH**

**Dimercaptosuccinic Acid (Succimer), cont.**

Succimer is only FDA approved for use in children. The recommended initial dose is 10 milligrams/kilogram or 350 milligrams/square meter every 8 hours for 5 days.

1. The dosing interval is then increased to every 12 hours for the next 14 days. Repeat course may be given if indicated by elevated blood lead levels. A minimum of 2 weeks between courses is recommended.
2. The capsule contents may be administered mixed in a small amount of food.

**Dimercaptosuccinic Acid (Succimer), cont.**

- ADULTS: 30 milligrams/kilogram/day in 3 divided doses for 5 days followed by 20 milligrams/kilogram/day in 2 divided doses for 14 days.
- Succimer may be used following EDTA and/or BAL after an interval of 4 weeks.

**Dimercaptosuccinic Acid (Succimer), cont.**

- **MONITORING PARAMETERS:**
  - Liver function test should be monitored before therapy begins and at 2 weeks
  - DMSA therapy was not adversely affected by borderline abnormal LFT in childhood lead poisoning in a prospective evaluation of 15 children (Kuntzelman & Angle, 1992).

**Arsenic**

- **Sources:**
  - Rodenticides
  - Herbicides (crabgrass killer)
  - Pesticides (Terro Ant Killer, Mol-Ex, etc)
  - Well water
  - Fire salts
  - Industry
  - Family, friends and spouses

**Arsenic**

Pentavalent Arsenic (As⁵⁺) vs. Trivalent Arsenic (As³⁺)
Arsenic

- **Initial Sxs:**
  - Garlic odor on breath
  - Dysphagia
  - Severe nausea and vomiting
  - Colicky abdominal pain
  - Profuse diarrhea
  - Hypotension

- **Additional symptoms with smaller doses:**
  - Severe headache
  - Vertigo
  - Periorbital edema
  - Skeletal muscle cramps

- **Additional symptoms with larger doses**
  - Cyanosis
  - Encephalopathy
  - ATN
  - Cardiomyopathy
  - Cardiac arrhythmias
  - CNS depression
  - Peripheral neuropathy

Chronic Arsenic Poisoning

- **Cutaneous manifestations:** flushing, hyperkeratosis, mees lines
- **Neuropathy:** glove and stocking (primarily sensory)
- **Hematologic findings:** anemia, leukopenia & thrombocytopenia
  - GI
  - Kidney
  - Cardiac

Laboratory Monitoring

- **Urine Arsenic Levels in a 24 hour collection**
  - >50 ug in a 24 hour period is excessive
  - Spot levels >200 ug/L is excessive
- **Treat at these levels if the patient is symptomatic**

Chelator Selection

- **Acute:** BAL
- **Chronic:** D-Penicillamine
- **DMSA (Difiercaposuccinic acid), Succimer**
  - approved for lead, effective for arsenic
- **DMPS (Dimercapstone propan sulfonate)**
  - effective for arsenic, acute and chronic, (used in Europe)
Arsenic Chelation Cases

<table>
<thead>
<tr>
<th>Date</th>
<th>U. Level (mg/L)</th>
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Sources:
- Paint chips & home renovation
- Auto exhaust
- Canned foods (solder)
- Water pipes
- Newspapers
- Lead weights
- Moonshine whiskey
- Earthenware & arts and crafts
- Natural remedies, ie, yesterday's folk medicine
- Industrial

Inorganic (lead salts) vs. Organic (tetraethyl lead)

Acute vs. Chronic

Mechanism: inhibits hemoglobin synthesis by inhibiting protoporphyrin formation

Acute exposure:
- N & V
- Abdominal pain
- Hemolysis
- Liver failure
- ATN

Chronic Exposure:
- Central nervous system
- Peripheral nervous system (motor)
- Heme
- GI
- Kidney
- Teratogen
Lead

Treatment Considerations:

- Blood levels >10 ug% are considered excessive
- >10<45 ug% perform mobilization test
- >45 ug% treat with DMSA ( Succimer ) or BAL or EDTA
- >70 ug% or encephalopathy, treat with two chelators, BAL and CaEDTA
- FEP ( Free Erythrocyte Protoporphyrin ) >50 ug%
  - Indicator of chronic consumption

### Lead Chelation Cases

#### 1st Admission - Organic Lead Poisoning Chelation

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#### Inorganic Lead Poisoning Chelation

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Case 1

A 3 Y.O. white male questionably swallowed approximately one ounce of Terro Ant Killer. He was referred to an emergency facility where gastric lavage was performed and activated charcoal and magnesium sulfate were administered. The patient was admitted overnight for observation and collection of a 24-hour urine specimen to be analyzed for arsenic. A CBC revealed an elevated white count of 24,000, urinalysis revealed a small amount of acetone. All other laboratory findings and physical exam were normal. He remained asymptomatic during the 24 hour observation period and since the history of ingestion was questionable, he was sent home while analysis of urine arsenic levels were pending. Results were reported 2 days following ingestion. Analysis revealed an arsenic excretion of 1023ug/24 hours. He remained well while at home, however, since urine arsenic excretion was elevated and the potential for late development of peripheral neuropathy existed, he was readmitted and chelated with BAL. Subsequent 24 hour urine collections revealed the following results: Day 4: 126ug; Day 6: 67ug; & Day 8: 13ug. The patient remained asymptomatic throughout his hospital stay and there were no signs of neuropathy at one month follow-up.
Case 2
A 4 Y.O. white male ingested between 1/2-1 oz. of Terro Ant Killer. The patient was referred to an emergency facility 2 hours after ingestion. Vomiting was induced with ipecac syrup. Activated charcoal and magnesium sulfate were given following emesis. Physical examination and laboratory results were normal. The child was observed for several hours in the emergency room and since he remained asymptomatic, was sent home with instructions to the parents to continue a 24 hour urine collection started in the emergency room. Results of the urine collection analysis returned 3 days later and revealed a urine arsenic concentration of 1600ug/L. The patient had remained asymptomatic so the attending physician decided to chelate with D-Penicillamine on an out-patient basis for 5 days. A 24 hour urine collection on the fifth day of chelation revealed a level of 47 ug/L. D-Penicillamine was discontinued. A urine collection performed 4 days after chelation therapy had been discontinued showed a urine arsenic concentration of 20ug/L. The child remained asymptomatic during chelation therapy and to 6 weeks follow-up. No signs of peripheral neuropathy were noted.

Cyanide Toxicity

Cyanide Antidote Kit
- Amyl nitrite 0.3 ml (forms Methemoglobin)
- Sodium nitrite 300 mg / 10 ml (forms Methemoglobin)
- Sodium Thiosulfate 12.5 grams / 50 ml (sulfur donor)

Case Summary
- History of Present Illness:
  - On the night of admission the patient accidentally ingested a few gulps of a metal polishing fluid containing Ajax, an Amway solution which was bought in Thailand and an unknown kind of pellet
  - These were mixed up approximately six months ago and had been sitting on a shelf next to a Hmong herbal remedy which the patient had meant to drink
  - The patient realized after a gulp or two that he had accidentally been handed the wrong bottle by his wife and tried to induce vomiting but collapsed within minutes of ingestion
  - Paramedics were called immediately and brought the patient to the emergency room where he was intubated, lavaged and given a first dose of charcoal

Sources
- Industrial
  - electroplating, mining, photography, rubber and chemical synthesis, pesticides/rodenticides, metal polish
- Plants (amygdalin-a cyanogen glycoside)
  - present in a wide variety (seeds of cherry, peach, apricot, etc)
- Drugs
  - nitroprusside, laetrile
- Combustion
  - smoke inhalation injuries
- False Nail Removers
  - delayed onset of toxicity and very potent
- Consumer Metal Polish

Mechanism
- Inhibits cytochrome oxidase and therefore oxidative phosphorylation
  - Blocks ATP production
  - Decreases oxygen utilization leading to cellular hypoxia and lactic acidosis
Symptoms
- Symptoms may shift rapidly
- CNS
  - early: headache, faintness, diaphoresis, anxiety/excitement
  - late: drowsiness/stupor, convulsions, paralysis, coma
- GI
  - salivation, nausea, vomiting
- Respiratory
  - tachypnea, dyspnea, smell of bitter almonds on breath, rapid onset of respiratory depression

Symptoms, cont.
- CV
  - early: hypertension, bradycardia
  - late: tachycardia, hypotension and CV collapse, ischemic ECG changes, arrhythmias
- Skin/ocular
  - skin may be brick red, retinal veins and arteries may be same color
- Lab
  - profound metabolic acidosis, $AG = VO_2$, bright red venous blood

Case Summary, cont.
- Physical Examination:
  - Physical exam on arrival in the Medical Intensive Care Unit showed a young thin, male who was intubated, agitated and combative with pink frothy sputum spewing out of the endotracheal tube.
  - The pulse was 136; blood pressure 136/79 with a respiratory rate of about 30.
  - Chest showed bilateral diffuse ronchi over the entire chest with poor air movement.
  - The extremities were pink and there was no bitter almond smell on the breath.
  - On neurologic exam the patient was initially very agitated and combative, dull's eyes were normal. Deep tendon reflexes were unobtainable.

Laboratory
- Arterial Blood Gas
- Central Venous Blood Gas
- Serum Lactate
- Electrolytes and Glucose
- Serum Cyanide (for confirmation only)

Case Summary, cont.
- Laboratory Data:
  - Serum electrolytes showed a sodium of 136, potassium 3.1, chloride 102, bicarbonate 11, glucose 518 (patient got an amp of Narcan), BUN of 25. Anion gap was 26.
  - Arterial blood gases early on showed pH of 7.12, $PCO_2$ of 58, and a $PO_2$ of 126.
  - Serum lactate was 18.6
  - serum osmolality calculated was 315 which was almost the same as the 318 measured value
  - serum was negative for ketones, barbiturates and salicylates
  - White blood count was 16.2 with a hemoglobin of 15.9
  - Chest x-ray showed diffuse pulmonary edema

Treatment
- Administer 100% oxygen, assisted ventilation (if required), bicarb for severe acidosis, fluids and vasopressors for hypotension and ECG
- Lilly Cyanide Antidote Kit
  - indications: antidotes should be used only in patients who have severe symptomology (ie, unresponsive, seizures, acidosis, unstable vitals). Restlessness anxiety, and tachypnea are not indications
  A. While preparing the sodium nitrite for infusion, break the amyl nitrite pears and hold under the patients nose for 30 seconds/minute. Will only give 5% MetHgb. Oxygen therapy should be continued at the same time
  B. Administer sodium nitrite 10ml of a 3%, NaNO, solution IV over 10-20 minutes. Pediatric dose is 0.2 mL/kg up to 10ml. Nitrates can cause extreme hypotension. Takes 30 min for peak formation of MetHgb. Goal is 15-30% MetHgb.
Treatment, cont.

C. Following the administration of the nitrite, inject adults with 80 ml of a 25% solution (12.5 g) of sodium thiosulfate. Pediatric dose - 5 ml Na₂S₂O₃ for every 1 ml of NaNO₂ given.

D. A second dose (usually 1/2 the first) may be administered 1/2 hour after first if there is an inadequate clinical response.

- After stabilization and initiation of antidote therapy, in cases of oral ingestion: gastric lavage (possibly with activated charcoal) should be performed followed by activated charcoal. SO₂ is contraindicated (rapid decreases in LOC can occur). Dermal exposure - wash skin and remove contaminated clothing.
- Hydroxycobalamin is also being used IV. Binds directly to CN to form cyanocobalamin.

Case Summary, cont.

- Hospital Course:
  - Within about 1 hour of the patient's ingestion we realized together with the ER staff that his ingestion may well have included cyanide which is often found in metal cleaning compounds and the patient therefore received the initial dose of the cyanide antidote kit.
  - He was started on Dopamine and was placed in reverse Trendelenburg position and his pressure progressively dropped into the 70’s.
  - His heart rate increased to about 170’s and the patient was switched to Dobutamine and Levophed both of which were run at 20 mcg/min. Despite this, his blood pressure continued to run in the 80’s and the patient became less responsive.
  - He received a second dose from the cyanide antidote kit and was started on charcoal hemoperfusion.
  - Eventually recovered and sent home.