EMERGENCY USE OF METAL CHELATORS

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DISCLOSURES

• There are no conflicts of interest to disclose
CHELATORS

• Google search using “chelation” reveals 1,640,000 sites

• Most sites involve testimonials such as:

CHELATION IN NATUROPATHIC PRACTICES

• Use of chelators increasing by naturopathic physicians

• Post-chelation testing common in this setting
  – Problematic
  – Not scientifically validated
  – ACMT position statement
OBJECTIVES

• Present chelators with regards to:
  – Accepted/conventional uses
  – Pharmacology
  – Adverse effects

• Will not discuss:
  – Non-standard uses of chelators
  – Non-FDA approved chelators (e.g. DMPS)
  – Heavy metal toxicity

CHELATORS TO BE DISCUSSED

• BAL
• DDC/Disulfiram
• Deferoxamine
• DMSA (succimer)
• D-penicillamine
• EDTA
• Prussian blue
CHELATORS

• Chelators: Molecule that forms a complex with a metal ion
  – Chelate derives from Greek word for “claw”
  – Chelator’s electrons binds with metal’s positive charge, forming covalent bonds
  – Many chelators bind via SH bonds

• The metal/chelator complex is subsequently excreted

CHELATORS

• Properties of ideal chelator:
  1) High affinity for toxic metal
  2) Low affinity for essential metals
  3) Minimally toxic
  4) Lipid soluble
  5) Highly absorbable from GI tract
CASE #1

• 3 children (15, 14, and 11 years) present complaining of joint pains

• All three were hypertensive with hypersensitivities of extremities with painful parasthesias

• History reveals patients were recently playing with a “silver liquid”

EXAM REVEALS DESQUAMATION
CASE #1

• Presumptive diagnosis of ___ toxicity with acrodynia made

• Treatment with succimer started

• Urine testing ultimately confirms diagnosis

MERCURY TOXICITY
SUCCIMER (DMSA)

- Succimer (meso-2,3 dimercaptosuccinic acid)

- FDA approved for treating lead poisoning with levels > 45 mcg/dL

- Off-labeled use: mercury, arsenic

SUCCIMER

- \( \text{C}_4\text{H}_6\text{O}_4\text{S}_2 \)

- Mercaptan-like odor

- Disulfide bonds responsible for metal chelation
SUCCIMER

• Available forms:
  – Renal imaging: 1.2 mg succimer and $^{99}$mTc
  – Chelation (Chemet®): 100 mg capsules

• Succimer results in increased excretion of:
  – Lead
  – Mercury
  – Arsenic
  – Zinc*

SUCCIMER: PHARMACOLOGY

• 20% oral bioavailability

• 95% protein bound (albumin) via disulfide linkages

• $T_{\text{max}}$ 3 hours

• 80-90% excreted in urine as mixed disulfides
SUCCIMER ADMINISTRATION

• Dosing:
  – Adults: 10 mg/kg q8h x5d, then q12h x14d
  – Pediatric: 350 mg/m³ q8h x5d, then q12h x14d

• Adverse effects:
  – GI irritation
  – 10% of patients with mild transaminitis
  – 4% of patients with rash

CASE #2

• 2 year old male with pica found on routine lab tests to have a whole blood lead level of 30 mcg/dL
LEAD TOXICITY

DOES THIS CHILD NEED CHELATION?

<table>
<thead>
<tr>
<th>Lead level (mcg/dL)</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 9</td>
<td>Retest in 1 year</td>
</tr>
<tr>
<td>10-14</td>
<td>Retest in 3 months; education</td>
</tr>
</tbody>
</table>
| 15-19               | - Retest in 2 months, education  
                        - If 15-19 twice, refer for case management |
| 20-44               | - Clinical evaluation  
                        - Education, environmental investigation |
| 45-69               | - Clinical evaluation/case mgt. within 48 h  
                        - Education, environmental investigation  
                        - Chelation |
| ≥ 70                | - Hospitalization  
                        - Immediate chelation  
                        - Education, environmental investigation |
### PEDIATRIC CHELATION REGIMEN

<table>
<thead>
<tr>
<th>Symptom/Level (mcg/dL)</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>BAL; 75 mg/m² q4h x 5days CaNa₂EDTA; 1500 mg/m²/d (continuous infusion or 2-4 divided IV doses x5d). Start 4h after BAL</td>
</tr>
<tr>
<td>Symptomatic or level &gt; 69</td>
<td>BAL; 50-75 mg/m² q4h x 3-5days CaNa₂EDTA; 1000-1500 mg/m²/d (continuous infusion or 2-4 divided IV doses x5d). Start 4h after BAL</td>
</tr>
<tr>
<td>Asymptomatic; level 45-69</td>
<td>Succimer 350 mg/m² tid x 5 d, then bid x 14d OR CaNa₂EDTA; 1000-1500 mg/m²/d (continuous infusion or 2-4 divided IV doses x5d)</td>
</tr>
<tr>
<td>Asymptomatic; level 20-44</td>
<td>Chelation generally not indicated. If chelation is performed, use succimer. - Exposure reduction</td>
</tr>
<tr>
<td>Asymptomatic; level &lt; 20</td>
<td>- Exposure reduction. Chelation not indicated</td>
</tr>
</tbody>
</table>

### BAL

- **BAL = dimercaprol = 2,3 dimercaptopropranol**
- Originally designed as an antidote to lewisite, an organoarsenical
- Later found that topical or IM BAL treated organoarsenical antibiotics
BAL

- C$_3$H$_8$OS$_2$
- Oily, colorless liquid
- Prepared as 10% solution in peanut oil to increase stability

BAL: AVAILABILITY

- Strong sulfur odor
- Each 3 mL ampule contains:
  - 100 mg/ml BAL
  - 200 mg/mL benzyl benzoate
  - 700 mg/mL peanut oil
BAL: USES

• BAL effectively binds arsenic, mercury, lead, and cadmium
  – Animals: Increases organic (alkyl) mercury and arsenic redistribution to brain
  – Effectively binds cadmium, but increases renal toxicity, and thus not recommended

BAL: OTHER USES

• Does not treat hemolysis from arsine gas, but may prevent complications

• Polonium 210
  • with D-penicillamine

• Can be used to treat copper toxicity
BAL: PHARMACOLOGY

• Widely distributed, but concentrates mostly in liver, kidney, and small intestine

• Majority of BAL eliminated in urine as metabolites

• Human volunteer studies:
  – Max arsenic excretion 2-4 hours after BAL

• BAL dissociates from metal in acidic urine; urinary alkalinization may be needed

BAL: PHARMACOLOGY

• Excreted via bile (liver) and urine (renal)

• Liver excretion permits BAL to be administered in Hg toxicity, even after renal failure occurs
BAL: ADVERSE EFFECTS

- Some adverse effects include:
  - Pain at injection site
  - Nausea/vomiting
  - Mucosal membrane irritation
  - Transient hypertension, and tachycardia
  - Sterile abscesses at injection site
  - Fever
- Most adverse effects occur within 30 min, and resolve by 50 minutes

BAL AND HEPATOTOXICITY

- Increased mortality when administered to rats with acute hepatotoxicity from CCl₄
- No clear data that hepatotoxicity is a contraindication for BAL
**BAL: CONTRAINDICATIONS**

- Potentially worsens toxicity with
  - Methylmercury (alkyl Hg)
  - Cadmium
  - Selenious acid
  - Thallium
- Peanut allergy
- ? G6PD (increases risk of hemolysis)

**BAL: DOSING**

- Ideal dosing regimen in humans unknown
- Arsenic:
  - 3 mg/kg IM q4h x 2d, then q12h x 7-10d
- Lead:
  - 4 mg/kg IM q4h x 2-7d
  - 75 mg/m² IM q4h
- Mercury (except alkyl mercury)
  - 5 mg/kg IM x 1d, then 2.5 mg/kg q12-24h x 10d
EDTA

• EDTA can exist in several forms
  – Calcium disodium EDTA
  – Also in disodium, trisodium, tetrasodium salts

• Only the calcium disodium form should be used medicinally

EDTA: HISTORY

• 1950: EDTA used investigationally for treatment of hypercalcemia

• 1952: calcium disodium added →
  – Effective chelator for lead
  – Not associated with risks of hypocalcemia
CALCIUM DISODIUM EDTA

- Also referred to as calcium edetate
- C_{10}H_{10}CaNa_{2}O_{8}
- Very water soluble

CALCIUM DISODIUM EDTA

- Stability constant of lead EDTA >> calcium EDTA, strong lead-EDTA chelate forms
- EDTA binds to lead, zinc
- IV or IM injection, but limited PO absorption
- T_{1/2} 2 hours
- Renal elimination with no metabolism
CALCIUM DISODIUM EDTA

- Decreased elimination of lead in setting of renal failure
- Large cumulative doses associated with proximal tubule damage
- Minimal, clinically inconsequential transaminitis can occur

CASE REPORT

Pediatric fatality secondary to EDTA chelation

ARLA J. BAXTER¹ and EDWARD P. KRENZELOK¹²

¹Pittsburgh Poison Center, University of Pittsburgh Medical Center, Pittsburgh, PA, USA
²School of Pharmacy and Medicine, University of Pittsburgh, Pittsburgh, PA, USA

- Calcium disodium EDTA well tolerated
- Several case reports of pediatric deaths when non-calcium forms used for chelation in autism
CALCIUM DISODIUM EDTA

- Administration can increase lead redistribution to brain
  - Pre-treatment with BAL at least four hours prior to EDTA reduces risk of redistribution

- Lead should be removed from GI tract prior to EDTA, as EDTA may increase absorption across GI mucosa

CALCIUM DISODIUM EDTA

- Should be diluted in NS or D5W

- 2-4g (30-50 mg/kg; 1-1.5g/m²/24 h) IV over 24 hours

- Continuous infusion should not exceed 5 days

- Lidocaine can be added if IM route utilized
D-Penicillamine

• Discovered in 1953 and first used for copper chelation in Wilson’s disease

• FDA approved indications:
  • Wilson’s disease
  • Cystinuria
  • Severe rheumatoid arthritis

• Enhances urinary excretion of lead
  – Unlike other chelators does not form stable bonds with lead
  – Possibly forms heterocyclic ring (sulfur and nitrogen binding to lead)

• Can increase urinary excretion of arsenic and mercury as well
D-PENICILLAMINE

• Primary toxicology use is for treatment of lead toxicity with lead levels 20-35 mcg/dL

• Avoid concurrent Fe

D-PENICILLAMINE

• Available in 125, 250 mg capsules

•Typical dosing 7.5 mg/kg bid

• Often needs to be mixed in juice or food due to bad taste and smell
D-Penicillamine: Adverse Effects

- 5-10% of patients discontinue therapy due to adverse effects
- Nausea, vomiting, decreased taste
- Leukopenia and rash occur in up to 7%
- Effects usually reversible

Case #3

- 5 year old male presents to ED with vomiting and profuse diarrhea after ingesting mother’s medications
- Exam notable for guiac positive stools, tachycardia, and dry mucosal membranes
CASE #3 (CONT.)

• Labs reveal:

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<tr>
<td>15</td>
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</table>

IRON TOXICITY

* Lanthanide series
* * Actinide series
DEFEROXAMINE

- Used for iron or aluminum chelation
- **C\textsubscript{25}H\textsubscript{48}N\textsubscript{6}O\textsubscript{8}**
- Highly water soluble

DEFEROXAMINE

- With iron toxicity, transferrin’s ability to bind iron is exceeded
- Binds in 1:1 molar ratio with non transferrin-bound iron
- Poor oral absorption
- Following IV administration, follows 2 compartment model, with t\textsubscript{1/2,\beta} of 3h
DEFEROXAMINE

- Metabolized, primarily to metabolite B, which is renally eliminated
- Relatively contraindicated in renal failure if not undergoing HD

DEFEROXAMINE: ADVERSE EFFECTS

- Four primary adverse effects described:
  1) Pulmonary syndrome
  2) Hypotension and shock
  3) Acute kidney injury
  4) Yersinia and mucor infections
DEFEROXAMINE: HYPOTENSION

- Primarily occurs with doses exceeding 15 mg/kg/hr

- Etiology likely multifactorial including:
  - Intravascular volume depletion from iron toxicity
  - Histamine release from DFO

DEFEROXAMINE: PULMONARY

- Pulmonary syndrome consists of:
  - Fever
  - NCPE with pulmonary infiltrates
  - Tachypnea
  - Eosinophilia

- Primarily occurs with prolonged infusions
DEFEROXAMINE: AKI

- Dog models demonstrate DFO decreases renal perfusion independently of blood pressure
- Intravascular volume expansion prior to DFO can prevent renal injury

DEFEROXAMINE AND THE LAB

- DFO’s chelating ability interfere with iron-binding reagents used in many iron assays
- Addition of reducing substance can be used with most standard lab measurements
  - Sodium hydrosulfite
  - Thioglycolic (mercaptoacetic acid)
- Atomic absorption or plasma emission spectrophotometric assays can be used
CASE #4

• 30 year old factory worker complains of shortness of breath, 12 hours after being exposed to fumes

• Found to have pulmonary edema

• He is started on diethyldithiocarbamate (DDC) for presumed nickel carbonyl toxicity
NICKEL CARBONYL

- Two antidotes available include:
  - Diethyldithiocarbamate (DDC)
  - Disulfiram (bis (diethylthiocarbamoyl))

- Disulfiram gets metabolized to DDC

DDC/DISULFIRAM

- In rat models, DDC at doses of 50-100 mg/kg decreased mortality from 73 to 8%

- Rat studies reveal “U” shaped mortality benefit with disulfiram
  - 500 mg/kg without benefit
  - 1000 mg/kg with improved mortality
  - 1500 mg/kg with increased mortality

-Recommended human dosing: 750 mg/kg PO twice daily
DISULFIRAM

• Inhibits several enzymes, including:
  – Aldehyde dehydrogenase 1, 2
  – Dopamine beta hydroxylase (DBH)

• Inhibition of DBH may occur as a result of copper chelation, a necessary cofactor for DPH

DISULFIRAM/DDC

• Other metals chelated by DDC:
  – Cadmium
  – Zinc
  – Nickel

• Increases CNS cadmium levels, and thus not recommended

• Increases absorption of nickel, disulfiram/DDC only recommended for nickel carbonyl
**CASE #5**

**PRUSSIAN BLUE**

- Initially synthesized as a pigment in 1704
- Also referred to as:
  - Fe₄[Fe(CN)₆]₃; Radiogardase® - insoluble
  - KFe[Fe(CN)₆]₃
  - K₃Fe[Fe(CN)₆]₃ Soluble (colloidal) Prussian blue
PRUSSIAN BLUE

- Normally, attaches to potassium ion
- Higher affinity for thallium or cesium
- Oral administration permits
  1) Binding to metal in gut $\rightarrow$ ↓ absorption
  2) Change concentration gradient $\rightarrow$ “gut dialysis”
  3) Interferes with enterohepatic recirculation

PRUSSIAN BLUE

- Insoluble form without PO absorption
- CN liberation is minimal, if any
- Thallium binding: soluble $>$ insoluble
- Cesium binding: insoluble $>$ soluble
- No human controlled trials exist
**PRUSSIAN BLUE**

- 150-250 mg/kg/d, divided 2-4 times daily

- Manufacturer recommendations:
  - Adults: 3g PO q8h
  - Pediatric: 1g PO q8h

- Often combined with a cathartic

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**SUMMARY**

<table>
<thead>
<tr>
<th>Metal</th>
<th>BAL</th>
<th>DDC</th>
<th>DFO</th>
<th>DMSA</th>
<th>D-Penn.</th>
<th>EDTA</th>
<th>Prussian blue</th>
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THANK YOU