Therapeutic Use and Misuse of Metal Chelation Therapy

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FOR AUDIO: CALL 866-740-1260/ ACCESS CODE: 764 4915#
DISCLOSURES

I have no financial relationships to disclose.

I will discuss the following off-label use in my presentation:

DMSA
DMPS
“Chelation therapy” is used extensively in the USA, but mostly without involvement of medical toxicology or occupational medicine specialists

2008 National Health Interview Survey of the CDC National Center for Health Statistics (scientific sampling of non-institutionalized US population, based on n = 32,000)

In 2007, 183,000 Americans, including 72,000 children, received “chelation therapy”

American Association of Poison Control Centers national database: 192 cases of chelation in 2007
What scientific evidence supports the rational use of chelation in the management of heavy metal intoxication?
World War I, Poison Gas, and the “Dew of Death”

Dichloro (2-chlorovinyl) arsine

“Lewisite”

Father J.A. Nieuwland

Capt. Winford Lee Lewis
London, WWII
Lewisite
Skin LD50 24 mg/kg (rat)
2, 3 - Dimercaptoopropanol

Dimercaprol  "British Anti-Lewisite"

BAL
% Decline in O\textsubscript{2} uptake (skin + pyruvate) after Lewisite (0.03mM), 1 hr

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>50 %</td>
</tr>
<tr>
<td>2-Mercaptoethanol (.54 mmol)</td>
<td>55</td>
</tr>
<tr>
<td>BAL (.27 mmol)</td>
<td>6</td>
</tr>
</tbody>
</table>

Survival (rats) after topical lewisite (≈ 35 mg/kg) (Treatment begun at 30 min post exposure)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>0/27</td>
</tr>
<tr>
<td>2-Mercaptoethanol</td>
<td>0/6</td>
</tr>
<tr>
<td>BAL (50 - 70 mg/kg inunction)</td>
<td>21/21</td>
</tr>
</tbody>
</table>

[Stocken & Thompson, Biochem J 40:535-548; 1946]
BAL increases urinary arsenic excretion in humans

Luetscher et al, J Clin Inv
25:534-540; 1946
1. In syphilis patients with arsenical dermatitis, BAL appeared to reduce the average duration of dermatitis (21.5 days vs 62.5 days) [Carleton et al, Quart J Med 17:49-85; 1948]

Prior to 6d
BAL rx

14 d after start
of BAL rx


<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th>LOS(d)</th>
<th>@Admit</th>
<th>@12h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without BAL</td>
<td>111</td>
<td>3</td>
<td>4.2</td>
<td>46.2%</td>
<td>29.3%</td>
</tr>
<tr>
<td>With BAL</td>
<td>42</td>
<td>0</td>
<td>1.6</td>
<td>47.6%</td>
<td>0%</td>
</tr>
</tbody>
</table>
BAL has high incidence of side effects

At high therapeutic doses (4 - 5mg/kg i.m. in peanut oil) as many as 2/3 of patients experience side effects which commonly include:

- Nausea and Vomiting
- Restlessness
- Hypertension
- Lacrimation and Salivation
- Fever
- Pain at injection site
2,3 dimercaptopropane sulfonic acid, Na salt
DMPS, unithiol
LD50 i.p. (m) 1371 mg/kg

2,3 dimercaptosuccinic acid, Na salt
DMSA, succimer
LD50 i.p. (m) 2500 mg/kg
### Therapeutic Index, ip, of Dimercapto Compounds in Mice Given an LD99 of NaAsO₂, sc

<table>
<thead>
<tr>
<th>Dimercapto compound</th>
<th>TI</th>
<th>LD50 (mmol/kg)</th>
<th>ED50 (mmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>meso-DMSA CI</td>
<td>369.0</td>
<td>13.73</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(11.36, 15.22)</td>
<td>(0.0262, 0.0466)</td>
</tr>
<tr>
<td>dl-DMPS CI</td>
<td>119.0</td>
<td>6.53</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(5.494, 7.706)</em></td>
<td><em>(0.0261, 0.0820)</em></td>
</tr>
<tr>
<td>dl-BAL CI</td>
<td>8.76</td>
<td>1.48</td>
<td>0.169</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>(1.11, 1.97)</em></td>
<td><em>(0.088, 0.325)</em></td>
</tr>
</tbody>
</table>

* TI = therapeutic index = LD50/ED50.

* Given 10 min after 0.15 mmol NaAsO₂/kg.
DMPS is more potent than DMSA as an arsenic antidote.

Reversal of arsenite inhibition of renal PDH enzyme activity in vivo.

Aposhian et al, ibid; 1984
Efficacy of chelation is enhanced by prompt administration following metal exposure.

Delayed chelation is diminished chelation.
Time - Dependent Efficacy of Chelation in Experimental Arsenic Poisoning

1. In Lewisite poisoned rabbits (Eagle et al, 1946):

One injection BAL  5 min post exposure:  100% survival
Multiple injections begun 6h post exp.  0%  "

2. In arsenite poisoned mice (0.14 mmol/kg sc) (Tadlock & Aposhian, 1980):

0.25mmol/kg DMSA

  at 60 min  79% survival
  at 120 min  55% survival
Randomized Placebo-Controlled Trial of 2,3-Dimercapto-1-propanesulfonate (DMPS) in Therapy of Chronic Arsenicosis Due to Drinking Arsenic-Contaminated Water

- 21 adults with chronic arsenic exposure (avg ≈ 20 y) and hyperpigmentation/hyperkeratosis
- Removed from As exposure < 3 mo; avg Urine As = 46 µg/L
- Single-blind randomization to 4 one-week courses of DMPS 100 mg qid (n=10) or placebo (n=10) over a 7 week period (in - hospital)

Primary outcome variable: Change in “clinical score” of multiple signs and symptoms assessed pre- and post-treatment
Skin biopsy pre- and post-treatment also assessed by blinded pathologist
<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline clinical score</th>
<th>Final clinical score</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMPS</td>
<td>8.90 ± 2.84</td>
<td>3.27 ± 1.73</td>
<td>0.0002</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.50 ± 1.96</td>
<td>5.40 ± 2.12</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Authors’ conclusion: DMPS “caused significant improvement in the clinical score of patients suffering from chronic arsenic toxicity”

Many limitations render findings inconclusive, including:

- More than half of clinical improvement resulted from non-blinded assessment of subjective parameters, including “lung disease” (cough, dyspnea, and rales/ronchi), and “weakness”
- Groups differed by gender: DMPS (9M, 2F); Placebo (5M, 5F)
- Subjects received nonrandomized “symptomatic treatment” (e.g. bronchodilators)
- Nonblinded clinical observer reported improvement in skin findings not confirmed by blinded skin biopsy assessment
MERCURY

Top of the Hit Parade for Eight Years

Richard A. Nickle
Environmental Health Scientist
Agency for Toxic Substances and Disease Registry
Acute Human Poisoning by Mercuric Chloride: Decreased Mortality with BAL Compared to Historical Controls

Longcope WT, Luetscher JA. Ann Intern Med 31:545-553; 1949

Table III

Patients poisoned by HgCl₂ after swallowing 10 gram or more treated within 4 hours:

- By old conventional methods
- By intramuscular injections of BAL
Chelators - Acute Hg intoxication

HgCl$_2$ 109 mg/kg p.o. to rats. Single dose chelator given 15 minutes later.

<table>
<thead>
<tr>
<th>Chelator</th>
<th>dose</th>
<th>Mortality*</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>9 / 10</td>
<td>90 %</td>
</tr>
<tr>
<td>BAL (i.p.)</td>
<td>400 µM (50 mg/kg)</td>
<td>5 / 10</td>
<td>50 %</td>
</tr>
<tr>
<td>DMSA (p.o.)</td>
<td>1600 µM (291 mg/kg)</td>
<td>4 / 10</td>
<td>40 %</td>
</tr>
<tr>
<td>DMPS (p.o.)</td>
<td>1600 µM (336 mg/kg)</td>
<td>0 / 10</td>
<td>0 %</td>
</tr>
</tbody>
</table>

*by day 14

Immediate DMPS prevents oliguric renal failure from i.v. HgCl$_2$ in rats

HgCl$_2$ 1.4 mg/kg (5 µmol). DMPS 54 mg/kg (250 µmol) i.v.

<table>
<thead>
<tr>
<th></th>
<th>No DMPS</th>
<th>Immediate DMPS</th>
<th>DMPS after 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>14.5</td>
<td>10.0</td>
<td>14.5</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.7</td>
<td>6.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Day 3</td>
<td>4.0</td>
<td>15.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Histopathology</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

n = 4 per group  
DMPS exceeds DMSA in reduction of renal Hg content after i.v. HgCl$_2$

[Planas-Bohne, Toxicology 19:275-278; 1981]

HgCl$_2$ (0.67 mg/kg) i.v. to rats.
After 24 h, chelators begun at 100 µmol/kg i.p. 4x/wk x 4 wk

Kidney Hg content (% of administered dose)

(n = 6 per group)

Control  11.57 ± 0.04
DMSA     5.73 ± 1.02
DMPS     0.71 ± .71
Antidotal benefit from DMPS is lost if treatment is delayed

HgCl$_2$ 1 mg/kg i.v. to rats. DMPS (150 µmol/kg) (32mg/kg) p.o. given qd x 5 beginning 6 or 24 hours later:

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality*</th>
<th>Percent</th>
<th>Survival time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8 / 18</td>
<td>44 %</td>
<td>19 days</td>
</tr>
<tr>
<td>DMPS @ 6h</td>
<td>1 / 18</td>
<td>6 %</td>
<td>29</td>
</tr>
<tr>
<td>DMPS @ 24h</td>
<td>6 / 18</td>
<td>33 %</td>
<td>22</td>
</tr>
</tbody>
</table>

* by 30 d

Reported Adverse Effects: DMPS, DMSA

- Allergic reactions, exanthems (1-10%)
- Mild gastrointestinal complaints (e.g. nausea) (1-10%)
- Isolated, reversible, slight increase in LFT's, decrease in wbc
- Increase in urinary Cu, Zn w/o Δ serum levels
Mobilization does not always equal excretion

Net redistribution of metal deposits, even when accompanied by increased excretion, may have undesirable consequences.
Dimercaprol (BAL) redistributes arsenic to the brain

Aposhian et al, ibid 1984
Dimercaprol (BAL) redistributes Hg$^{2+}$ to the brain

Berlin M, Rylander R. J Pharm Exp Ther 146:236-240; 1964
DMPS increases urine mercury excretion in acute Hg vapor intoxication  [Cichini GM et al. Intensivmed Notf Med 26:303-306; 1989]

- 19 caisson workers drilling a subway tunnel developed acute symptomatic Hg° vapor intoxication after a mean of 27h (range ≈ 8 - 40h) exposure.
- Subjects randomized to DMPS (100 mg or 200 mg tid) or D-Pen 150 mg tid
Following subacute exposure to Hg vapor, DMPS and DMSA reduce Hg concentration in kidneys but not the brain

Rats (n = 8 per group) underwent 14 days inhalation to Hg⁰ (244 µg/m³) Seven days later, treated for 5 days with 1 mmol/kg/day po DMSA or DMPS, then sacrificed 24 hours later.

<table>
<thead>
<tr>
<th>Group</th>
<th>Hg concentration (µg/100g body wt)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidney</td>
<td>Brain</td>
</tr>
<tr>
<td>Hg⁰ only</td>
<td>2.78 ± 0.60</td>
<td>0.088 ± 0.017</td>
</tr>
<tr>
<td>DMSA</td>
<td>0.46 ± 0.20</td>
<td>0.076 ± 0.008</td>
</tr>
<tr>
<td>DMPS</td>
<td>0.10 ± 0.02</td>
<td>0.098 ± 0.030</td>
</tr>
<tr>
<td>Control (n=4)</td>
<td>0.17 ± 0.15</td>
<td>0.0022 ± 0.0005</td>
</tr>
<tr>
<td>(no Hg, no chelator)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Buchet JP, Lauwerys RR. Toxicology 54:323-333; 1989
Chelation in the Management of Lead Intoxication

Introduction of CaNa$_2$EDTA in 1950s associated with a temporal decline in mortality from lead encephalopathy, but no randomized clinical trials conducted, and supportive care (ICU, mannitol, corticosteroids) was concurrently improved.

In animal models of acute, high dose lead intoxication, chelating agents alone have neither decreased mortality nor averted nonlethal effects (e.g. Hofmann & Segewitz, 1975; Xu & Jones, 1988).
Chelation for Lead Intoxication

- Chelating agents decrease lead concentration in blood and certain tissues, and greatly accelerate urinary lead excretion

  $\text{CaNa}_2\text{EDTA}$ (intravenous or intramuscular)
  Succimer (DMSA) (oral)
  DMPS (oral or intravenous)

**HOWEVER,**

- There are no randomized, placebo controlled trials of chelation that indicate it improves the therapeutic outcome of patients
The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead [Rogan et al, NEJM 2001; 344:1421-6]

780 children (12 - 33 mo.) with PbB 20 to 44 ug/dL enrolled in randomized, placebo-controlled, double-blind trial of up to three 26 day courses of treatment with succimer (DMSA).

No longterm benefit on blood Pb or neuropsychological outcome
Succimer Chelation Improves Learning, Attention, and Arousal Regulation in Lead-Exposed Rats but Produces Lasting Cognitive Impairment in the Absence of Lead Exposure [Stangle DE et al, EHP. 115:201-209; 2007]

3 x 2 factorial design: 3 levels of exposure (hi, med, none) and 2 levels of treatment (succimer, placebo); 20 animals per group

High-Pb: lactational exposure PND 1-17, then 300 ppm Pb in water to day 30. PbB peak ≈ 100-140 µg/dL

Mod-Pb: lactational exposure PND 1-17, then 20 ppm Pb in water to day 30. PbB peak ≈40-60 µg/dL

Chelation groups: beginning on PND 30, 50 mg/kg/d po x 1 week, then 25 mg/kg/d x 2 wks
Chelation markedly decreased blood and brain Pb

Brain Pb in High-Pb-succimer group similar to nonchelated Mod-Pb group

Stangle et al, 2007
Multiple types of behavioral testing (blinded) begun on PND 62 over next several months

Visual discrimination: poke nose into port corresponding to illuminated LED and get food pellet (learning)
+ variable delay; + variable duration (attention)
+ olfactory distraction (selective attention)
Performance after an error on prior trial (measure of arousal or emotional regulation)
Short period of early-life Pb exposure causes enduring deficits:
Mod-Pb: impairment in learning
High-Pb: impairment in learning, plus attention, arousal control

*Succimer chelation improved learning, particularly in Mod-Pb group*

Stangle et al, 2007
Why a different outcome in the Stangle chelation study (rats) vs. the TLC study (children)?

- Succimer chelation dose was higher in Stangle study than in TLC trial

- Rat chelation protocol may have achieved greater reductions in blood and bone lead than TLC protocol; at time of cognitive testing, there were differences in blood lead among rodent groups, but not in the children

- Human CNS is more sensitive to adverse effects of lead
Succimer treatment of rats not exposed to Pb resulted in a marked deterioration of learning and attention.

The learning deficits caused by succimer alone were of same magnitude as the deficits caused by high lead exposure.

Stangle et al, 2007
Why a different outcome in the Stangle chelation study (rats) vs. the TLC study (children)?

• Succimer chelation dose was higher in rat study than in TLC trial

• Rat chelation protocol may have achieved greater reductions in blood and bone lead than TLC protocol

• Human CNS is more sensitive to lead

• Succimer alone might cause significant risks, and should not be used indiscriminantly
There may still be a rational role for chelation in the treatment of:

- *all children with BLL ≥ 45 µg/dL*,
- *symptomatic adults with BLL > 50 ug/dL*,
- *asymptomatic adults with BLL > 100*

In addition to *possibly* diminishing further translocation of lead into the CNS and hastening resolution of symptoms, chelation in patients with very high blood lead levels may avert progression to lead encephalopathy, a potentially life-threatening complication.
A recent case from Los Angeles

A 7 y.o. child presented to a physician complaining of fatigue.

A DMSA provocation test for metals in urine was ordered, as was a blood lead test.

The urine challenge test yielded a 6 hour urine with a lead concentration of 84 μg/gCr. This was reported as “very elevated” compared to a laboratory “reference range” of <5 μg/gCr. The reference range was noted to reflect “a healthy population... under nonprovoked conditions.”

The blood lead concentration was reported as 4 μg/dL.

Parents were informed that the child had “acute lead poisoning” and was in need of chelation.
Despite a follow-up blood lead test one month later at a different laboratory of 1.0 μg/dL, the child underwent chelation with DMSA.

Over the next 2 years, 15 courses of DMSA were given.

The DMSA was sold directly to the parents of the patient by health care providers, who obtained it as an OTC “supplement” from distributors who cater to the alternative medicine community.
Captomer-250 45 Capsules
by Thorne

List Price: $118.00
Price: $109.99 & this item ships for FREE with Super Saver Shipping. Details
You Save: $8.01 (7%)

Only 1 left in stock.
Sold by Fast Supplements and Fulfilled by Amazon. Gift-wrap available.
Want it delivered Wednesday, October 17? Order it in the next 17 hours and 32 minutes, and choose One-Day Shipping at checkout. Details

Product Description

DMSA (meso-2,3-dimercaptosuccinic acid), a sulfhydryl-containing compound, binds to metallic elements and is of significant benefit in maintaining a normal balance of metal elements in the body. Thorne provides DMSA in both 100 mg and 250 mg capsules.
The use of post-chelation challenge urinary metal excretion to identify patients who will derive therapeutic benefit from chelation has not been validated.

A comparison of a provoked urine result to a urine “reference range” derived from a non-provoked population will virtually guarantee an “elevated” result..

This problem is further compounded when results from children are compared to creatinine adjusted values obtained from adults.

Note: the quotient “μg X / g Creatinine” will be elevated not only if X is high, but also if urine creatinine is low. Creatinine adjustment, when performed, should always be compared to age and gender appropriate controls.
American College of Medical Toxicology Position Statement on Post-Chelator Challenge Urinary Metal Testing (2009):

“…post-challenge urinary metal testing has not been scientifically validated, has no demonstrated benefit, and may be harmful when applied in the assessment and treatment of patients in whom there is concern for metal poisoning.”

US CDC (2012):

“Some practitioners administer chelators prior to testing urine for the presence of heavy metals. The evidence does not support testing for heavy metals in this manner.”
Summary

1. Chelation with DMSA, DMPS, or BAL has therapeutic benefit in acute intoxication by inorganic arsenic or inorganic mercury salts if administered promptly (within minutes to hours)

2. DMPS and DMSA have a higher therapeutic index than BAL, and unlike BAL do not redistribute As or Hg to the brain

3. Although chelation for chronic intoxication by As or Hg may accelerate metal excretion and diminish concentration in some organs, therapeutic efficacy in terms of decreased morbidity and mortality is largely unestablished.

4. Chelation for high dose lead intoxication is rationale to possibly avert or mitigate encephalopathy; potential therapeutic efficacy at low to moderate BLLs is uncertain
5. Post–chelation challenge tests that measure metals in urine have not been validated as a method to identify patients who will benefit from chelation. Results are often presented in a potentially misleading manner.
Thank you!

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