The Weight of the Evidence: The Role of Chelation in the Treatment of Arsenic and Mercury Poisoning

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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 - Dimercaptopropanol

Dimercaprol  "British Anti-Lewisite"
% Decline in O₂ uptake (skin + pyruvate) after Lewisite, 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 (≈ 30 mg/kg)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>0/6</td>
</tr>
<tr>
<td>2-Mercaptoethanol</td>
<td>0/6</td>
</tr>
<tr>
<td>BAL (50 - 70 mg/kg inunction)</td>
<td>8/8</td>
</tr>
</tbody>
</table>

[Stocken & Thompson, 1946]
BAL increases urinary arsenic excretion in humans

Luetscher et al, 1946
Human Arsenic Intoxications Treated with BAL: Comparison to Untreated Historical Controls

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]


<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Deaths</th>
<th>LOS(d)</th>
<th>% Symptomatic @Admit</th>
<th>% Symptomatic @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 dimercaptopropionate 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
<table>
<thead>
<tr>
<th>Dimercapto compound</th>
<th>TI $^a$</th>
<th>LD50 (mmol/kg)</th>
<th>ED50 $^b$ (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>(5.494, 7.706)</td>
<td>(0.0261, 0.0820)</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>(1.11, 1.97)</td>
<td>(0.088, 0.325)</td>
</tr>
</tbody>
</table>

$^a$ TI = therapeutic index = LD50/ED50.

$^b$ Given 10 min after 0.15 mmol NaAsO$_2$/kg.

Aposhian et al, 1984
DMPS is more potent than DMSA as an arsenic antidote

Reversal of arsenite inhibition of renal PDH enzyme activity in vivo

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

Delayed chelation is diminished chelation
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 [Guha Mazumder et al, Clin Toxicol 39:665-674; 2001]

- 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
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

86 control cases
41 cases treated by BAL

[Table showing data]
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

[Nielson & Anderson, 1991]
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  [Wannag & Aaseth, 1980]
DMPS exceeds DMSA in reduction of renal Hg content after i.v. HgCl₂

[Planas-Bohne, 1981]

HgCl₂ (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

[Planas-Bohne, 1977]
Reported Adverse Effects: DMPS, DMSA

- Allergic reactions, exanthesms (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, 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 Hgº (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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td>Hgº only</td>
<td>2.78 ± 0.60</td>
</tr>
<tr>
<td>DMSA</td>
<td>0.46 ± 0.20</td>
</tr>
<tr>
<td>DMPS</td>
<td>0.10 ± 0.02</td>
</tr>
<tr>
<td>Control (n=4)</td>
<td>0.17 ± 0.15</td>
</tr>
<tr>
<td>(no Hg, no chelator)</td>
<td></td>
</tr>
</tbody>
</table>

Buchet JP, Lauwerys RR. Toxicology 54:323-333; 1989
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.