REVIEW OF THE COMPARATIVE EFFECTIVENESS AND SAFETY OF CALCIUM DISODIUM EDETATE AND PENICILLAMINE FOR THE TREATMENT OF LEAD POISONING IN CHILDREN

Report

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1. **Background**

In October 2007, the Expert Committee on the Selection and Use of Essential Medicines noted that lead poisoning was a significant public health problem in many developing countries. Treatment of lead poisoning, therefore, was considered essential to include on the Essential Medicines List for Children. While penicillamine and sodium calcium edetate are both licensed for this indication, there was no basis for the Subcommittee to determine which, if any, was superior. Both were therefore included, and a review of efficacy and safety was requested.i

The Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines reiterated the need for a synthesized or systemic review of the safety and effectiveness of penicillamine compared to sodium calcium edetate for the treatment of lead poisoning in the fall of 2008.ii The current document provides a review of the evidence to inform key stakeholders of the efficacy and safety or penicillamine and sodium calcium edetate in the treatment of lead poisoning in pediatric patients.

2. **International Non-propriety Name (INN, generic name) of the medicine**

<table>
<thead>
<tr>
<th>INN:</th>
<th>Calcium disodium edetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name:</td>
<td>edetate calcium disodium</td>
</tr>
<tr>
<td>Chemical name:</td>
<td>([N,N'-1,2-ethanediyl-bis[N-(carboxymethyl)-glycinato]][(4-)-N',O',O',ON,ON']-, disodium, hydrate, (OC-6-21)-Calciate(2-)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INN:</th>
<th>d‐penicillamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name:</td>
<td>penicillamine</td>
</tr>
<tr>
<td>Chemical name:</td>
<td>(2s)-2-amino-3-methyl-3-sulphanylbutanoic acid</td>
</tr>
</tbody>
</table>

3. **Formulation**

- **Calcium disodium edetate:** 200 mg calcium disodium edetate in 1 mL; vials of 2.5 mL and 5 mL
- **Penicillamine:** 250 mg penicillamine capsules; 30 capsules per package
  250 mg penicillamine tablets, scores; 30 tablets per package
  A 50 mg/mL suspension may be made by mixing sixty 250 mg capsules with 3 g carboxymethylcellulose, 150 g sucrose, 300 mg citric acid, parabens (methylparaben 120 mg, propylparaben 12 mg, propylene glycol qs ad to 100 mL), and purified water to a total volume of 300 mL; cherry flavor may be added. Stability is 30 days refrigerated. (DeCastro Hosp Pharm 1977)

4. **Global burden of disease**

It was estimated that in 2000, 120 million people worldwide had blood lead levels of 5-10 mcg/dL and approximately the same number had levels above 10mcg/dL. About 40% of children had blood lead levels above 5mcg/dL and 20% above 10 mcg/dL, with 97% of these children living in developing regions. Less then 10% of children had levels above 20 mcg/dL but, 99% of those that did lived in developing regions.iii

In the United States, the National Health and Nutrition Examination Survey has documented a steady decline in the number of children 1-5 years old with blood lead levels > 10 mcg/dL 77.8%
The dramatic decline has resulted in improved health and productivity, with an estimated averted health cost of $312 billion.\textsuperscript{v vi}

5. \textbf{Indications for use}

5.1 Calcium disodium edetate

The United States Food and Drug Administration (FDA) has approved calcium disodium edetate in both adults and children for the reduction of blood levels and depot stores of lead in lead poisoning (acute and chronic) and lead encephalopathy.\textsuperscript{vii}

5.2 Penicillamine

The indications for penicillamine are many and varied. In the case of adults, the FDA approved indications for penicillamine include: cystinuria, severe and active rheumatoid arthritis that has failed to respond to conventional therapy, and Wilson’s Disease. Penicillamine is not approved for the treatment of lead poisoning by the FDA, nor is there any approved indication for use in pediatric patients.\textsuperscript{viii}

6. \textbf{Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostic or treatment facilities and skills)}

6.1 Dosage regimens

<table>
<thead>
<tr>
<th>Indication(s)</th>
<th>Dosage</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium disodium edetate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Symptoms of lead encephalopathy and/or blood lead level > 70 mcg/dL\textsuperscript{*} | 250 mg/m\textsuperscript{2}/dose IM every 4 hours  
50 mg/kg/day IV as a continuous 24 hour infusion OR  
1-1.5 gm/m\textsuperscript{2} IV as either an 8 to 24 hour infusion or divided into 2 doses every 12 hours | 5 days, wait a minimum of 2 days with no treatment before considering a repeat course |
| Symptomatic lead poisoning without encephalopathy or asymptomatic with blood lead level > 70 mcg/dL\textsuperscript{†} | 167 mg/m\textsuperscript{2}/dose IM every 4 hours  
1 gm/m\textsuperscript{2} IV as an 8 to 24 hour infusion or divided every 12 hours | 3-5 days                                                                                   |
| Asymptomatic children with blood lead level 45-69 mcg/dL                    | 25 mg/kg/day IV as an 8 to 24 hour infusion or divided every 12 hours     | 5 days  
Depending upon the blood lead level, additional courses may be necessary; repeat at least 2-4 days, preferably 2-4 weeks, apart |

<table>
<thead>
<tr>
<th>Penicillamine</th>
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<th></th>
</tr>
</thead>
</table>
| Lead poisoning                                                              | 20-30 mg/kg/day orally in 3-4 divided doses, maximum dose is 1.5 gm/day  
Start at 25% of total dose and increase gradually to full dose over 2-3 weeks | 4-12 weeks  
Depends upon pretreatment blood lead level |
| Moderate lead poisoning (blood lead level 20-40 mcg/dL)                     | 15 mg/kg/day orally in 2 divided doses                                | 4-12 weeks  
Depends upon pretreatment blood lead level |

Abbreviations: mg = milligram; gm = gram; kg = kilogram; m\textsuperscript{2} = meters squared; IM = intramuscular; IV = intravenous
* Use in conjunction with dimercaprol
† Recommended to be used with dimercaprol until blood lead level is < 50mcg/dL

6.2 Reference to existing WHO and other clinical guidelines

The United States Centers for Disease Control (CDC) recommends the following for children with confirmed elevated blood lead concentrations.

Table 6.2 CDC recommendations for children who have confirmed (venous) elevated blood lead concentrations

<table>
<thead>
<tr>
<th>Blood Lead Concentration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14 mcg/dL</td>
<td>Lead education Follow-up blood lead monitoring within 1 month</td>
</tr>
<tr>
<td>15-19 mcg/dL</td>
<td>Lead education Follow-up blood lead monitoring within 1 month Proceed according to actions for 20-44 mcg/dL if a follow-up blood lead concentration is in this range after at least 3 months; or blood level increases</td>
</tr>
<tr>
<td>20-44 mcg/dL</td>
<td>Lead education Follow-up blood lead monitoring within 1 week Complete history and physical Laboratory work (hemoglobin, hematocrit, iron) Environmental investigation Neurodevelopmental monitoring Abdominal radiography (if particulate lead ingestion is suspected, with bowel decontamination if indicated)</td>
</tr>
<tr>
<td>45-69 mcg/dL</td>
<td>Lead education Follow-up blood lead monitoring within 48 hours Complete history and physical Laboratory work (hemoglobin, hematocrit, iron, free erythrocyte protoporphyrin or zinc protoporphyrin) Environmental investigation Lead hazard reduction Neurodevelopmental monitoring Abdominal radiography (if particulate lead ingestion is suspected, with bowel decontamination if indicated) Chelation therapy</td>
</tr>
<tr>
<td>≥70 mcg/dL</td>
<td>Hospitalize and commence chelation therapy Follow-up confirmation of blood level immediately Proceed according to actions for 45-69 mcg/dL</td>
</tr>
</tbody>
</table>

The American Academy of Pediatrics (AAP) makes specific recommendations for drug treatment based upon the CDC guidelines for venous blood lead level. If the blood lead level is greater than 45 mcg/dL and exposure source has been controlled, treatment should begin with oral succimer. Children with symptoms of lead poisoning or with a blood lead level greater than 70 mcg/dL or who are allergic or react to succimer should be hospitalized and receive treatment with calcium disodium edetate. The safety and efficacy of penicillamine has not been established and is reserved as a third line agent.
7. **Summary of efficacy in the treatment of lead poisoning**

7.1 Penicillamine
7.1.1 Literature search

Medline (1950-September 2010), the Cochrane Database of Systematic Reviews and the World Health Organization website were searched to identify all published papers and trial reports that described the use of penicillamine for lead poisoning in children. Search terms used to identify studies included: penicillamine, lead, poisoning, infant, child, pediatrics, neonates and children. Medical subject headings (MeSH) were used when available or appropriate. Reference lists of retrieved articles were reviewed to identify any potentially relevant studies not identified during the database searches.

The literature search did not identify any prospective randomized trials. Two prospective reports analyzed the use of penicillamine in children with small lead burdens.xii xiii A retrospective cohort addressed the efficacy of penicillamine in children for lead poisoning; another retrospective analysis addressed adverse events.xiv xv

7.1.2 Efficacy

Shannon et al studied the use of penicillamine in 27 children. The mean age was 33 months (range 14-72). Patients received penicillamine as a crushed tablet or opened capsule dosed 15-30 mg/kg daily. Clinic visits were made every two to four weeks for measurement of blood lead levels, erythrocyte protoporphyrin levels, hematologic index and urinalysis. Mean treatment duration was 10 weeks (range, 4-20 weeks). Results are shown in table 7.1. Toxicity was limited to a transient decrease in white blood cell count in one patient. The authors concluded that penicillamine efficacy extends beyond that of calcium disodium edetate at low lead levels.xii

| Table 7.1 Clinical Course of 27 Children Receiving Penicillamine for Lead Poisoning |
|-----------------------------------|-----------------|
|                                  | Mean       | Range    |
| Peak Blood Lead Level            | 37         | 26-53    |
| Peak Erythrocyte protoporphyrin  | 138        | 37-485   |
| Pretreatment Blood Lead Level    | 26         | 21-30    |
| Post-treatment Blood Lead Level* | 12         | 9-15     |
| Pretreatment Erythrocyte protoporphyrin | 73       | 15-318   |
| Post-treatment Erythrocyte protoporphyrin* | 36   | 20-62    |

* P<0.001 by two-sided Student's t-test

Marcus prospectively analyzed the effect of penicillamine on 67 children with initial lead levels between 40 and 60 mcg/dL or an abnormal lead mobilization test. All patients received 30 mg/kg/day of penicillamine divided twice daily on an empty stomach for three months. There was an average decrease in blood lead level of 27% during the first two weeks of treatment. Blood lead levels continued to drop throughout the following three months, but after six weeks an apparent steady state lead level seemed to be reached. There was no significant change in lead levels between the sixth week and the 12th week of treatment.xiii

No serious adverse effects were reported for any patient during the treatment period. Eleven patients developed eosinophilia, which resolved with interruption of therapy, most tolerated reinstitution of therapy without further problems. Nineteen patients developed proteinuria (5mg/dL or greater); no child had significant proteinuria on 24 hour urine collection. Blood-urea-nitrogen was elevated in 34% of patients and remained elevated until therapy was withheld. All cases resolved to less than 15 mg/dL after withdrawal of treatment. Concurrent serum creatinine levels were normal. The author concluded that penicillamine is useful in the
treatment of moderate lead poisoning if appropriate monitoring parameters are applied for adverse effects.\textsuperscript{xiii}

Shannon \textit{et al} conducted a retrospective cohort of patients with blood lead levels ranging from 25-40 mcg/dL either treated with penicillamine or not treated. Patients must not have received any chelation therapy in the 12 weeks prior to the observation period. Three time periods were recorded: an observation period beginning 1-3 months prior to chelation, a chelation period, and a 28 day post chelation or rebound period. Control patients had lead levels measured at the same time periods though none received any treatment. Results are listed in table 7.2.\textsuperscript{xiv}

### Table 7.2 Lead levels in treated and control patients

<table>
<thead>
<tr>
<th></th>
<th>Treated Patients (n = 84)</th>
<th>Control Patients (n = 37)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-observation level</td>
<td>34</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-chelation level</td>
<td>33</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Post-chelation level †</td>
<td>22</td>
<td>32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Rebound‡</td>
<td>27</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

NS = not significant; N/A = not applicable
* Treated versus control
† p<0.001 in treated patients pre-chelation versus post-chelation
‡ p<0.01 in treated patients post-chelation versus rebound

Penicillamine was administered by parents in two or three divided doses at a total dose of 25-35 mg/kg daily. Mean age was 3 years (range 1-15 years). Seventy-five patients received 84 courses of penicillamine treatment. Eight subjects (10 \%) had blood lead levels that either did not change or increased. Twenty-nine adverse reactions were reported in 28 patients. Leukopenia was the most common adverse event occurring in eight patients; in seven patients, the white blood cell count normalized within four weeks without changing therapy. Other adverse events included thrombocytopenia, rashes (urticarial, maculopapular, and erythema multiforme), urinary incontinence, abdominal pain, diarrhea, microscopic hematuria, and abnormal liver enzymes. Chelation was stopped in eight subjects due to adverse events. The authors concluded that penicillamine was effective for low-level lead poisoning in course as little as 6-8 weeks and may require more careful monitoring in certain patients.\textsuperscript{xiv}

### 7.2 Calcium disodium edetate

#### 7.2.1 Literature search

Medline (1950- September 2010), the Cochrane Database of Systematic Reviews and the World Health Organization website were searched to identify all published papers and trial reports that described the use of calcium disodium edetate for lead poisoning in children. Search terms used to identify studies included: calcium disodium edetate, lead, poisoning, infant, child, pediatrics, neonates and children. Medical subject headings (MeSH) were used when available or appropriate. Reference lists of retrieved articles were reviewed to identify any potentially relevant studies not identified during the database searches.

The literature search identified one prospective controlled trial comparing treatment with calcium disodium edetate to no treatment in children with moderate lead poisoning.\textsuperscript{xvi} A second prospective trial analyzed the effect of declining blood levels on cognitive changes in moderately lead poisoned children; some patients did receive calcium disodium edetate, but this trial was not controlled.\textsuperscript{xvii} Two retrospective trials were also identified.\textsuperscript{xviii xix}
7.2.2 Efficacy

Markowitz et al. assessed the relationship between calcium disodium edetate chelation and measure of lead burden and toxicity in children with moderate lead poisoning. This single center study enrolled 201 patients. Patients were excluded if they had received chelation therapy previously or had blood lead levels outside of the range 25-55 mcg/dL. All patients received a lead mobilization test (LMT), those with positive tests received chelation treatment with, those with a negative LMT were the control group. Seventy-one patients received treatment, 103 patients were in the control group. Results are shown in table 7.3

<table>
<thead>
<tr>
<th></th>
<th>Blood Lead (mcg/dL)</th>
<th>Bone Lead, CNET</th>
<th>EP (mcg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Rx</td>
<td>Rx</td>
<td>P</td>
</tr>
<tr>
<td>Raw Change</td>
<td>-2.5</td>
<td>-7.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted for initial level</td>
<td>-3.9</td>
<td>-5.2</td>
<td>0.21</td>
</tr>
<tr>
<td>Raw Change (matched for initial level)</td>
<td>-4.1</td>
<td>-5.8</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*The mean changes in blood lead, bone lead, and EP concentration are shown in their original metrics; the significance tests shown are of the square root transformation of bone lead and the natural logarithmic transformation of EP. CNET = corrected net counts.

The effect of calcium disodium edetate chelation therapy on blood lead levels over the observation period is not specific. The apparent effect of chelation on blood lead levels may be accounted for based on the higher initial concentration of blood lead in the treatment group versus the untreated group. When controlled for initial lead level, there is no difference between groups. The authors concluded that there is now sufficient doubt about efficacy of calcium disodium edetate to warrant a randomized controlled trial in moderately lead-poisoned children, but it would be premature to withhold treatment in patients with a positive LMT.

Ruff et al analyzed whether chelation therapy or biochemical changes during a lead-lowering intervention were associated with changes in cognitive function. Patients with a blood lead level between 25-55 mcg/dL were eligible for enrollment. All patients were given a LMT, those with positive tests received treatment with calcium disodium edetate, those with negative tests were controls. Cognitive function was measured at baseline, at seven weeks and at six months.

There were no significant changes in cognitive function in the treated group between baseline and seven weeks or six months. There were also no significant differences between the treated and untreated groups at baseline, seven weeks or six months. The authors postulated the lack of effect of chelation may have been related to other abatement procedures in the home, reduction or elimination of exposure, or that all patients received a LMT.

O'Connor conducted a retrospective chart review of 72 patients that received either calcium disodium edetate alone or in conjunction with British anti-Lewisite (BAL) at single center in the United States. Patients were eligible for this study if they had an initial blood lead level between 50-60 mcg/dL and had at least one follow-up visit where a lead level was measured. Twenty-nine patients received calcium disodium edetate alone and 43 received combination therapy.
At the first post-chelation follow-up (one to three weeks after treatment) patients that received calcium disodium edetate alone had a significantly greater decrease in lead concentration compared to combination therapy. At six months, there was no difference in percent change between the two groups. Patients that received combination therapy had significantly more vomiting and increases in transaminases. The author concluded that combination therapy did not decrease the need for repeat chelation treatments in patients with initial blood lead levels between 50-60 mcg/dL and increased the number of adverse events. Combination therapy should be reserved for patients with blood lead levels >70 mcg/dL or signs of encephalopathy.\textsuperscript{xix}

Bradley \textit{et al.} retrospectively analyzed the mental development of 18 children after treatment with either BAL or calcium disodium edetate for lead poisoning. There were nine patients in each group. Mean follow-up was 3.77 years for the BAL group and 3 years for the calcium disodium edetate group. Overall, there was no significant residual intelligence deficit for the study population. Visual-motor deficit was the only prominent residual in all patients and appeared to be more frequent in the BAL treated group. This deficit generally corresponded to severity of illness.\textsuperscript{xviii}

7.3 Comparative efficacy of penicillamine and calcium disodium edetate

Moncrieff \textit{et al} published a case series of pediatric patients comparing parenteral calcium disodium edetate and oral penicillamine in the treatment of lead poisoning. Twenty patients were described, age range 1-5 years with blood lead levels ranging from 40 – 380 mcg/dL. All patients in this case series with blood lead levels greater than 80 mcg/dL received parenteral calcium disodium edetate (either intramuscularly or intravenously). The authors concluded that intravenous calcium disodium edetate increased urinary excretion of lead far greater than oral penicillamine. Since intravenous calcium disodium edetate produces the maximum urinary excretion rates of lead, it should be used in cases of severe poisoning. The authors also concluded that penicillamine produces an effective rise in urinary lead excretion, which over the same period of time compares favorably with intramuscular calcium disodium edetate. Penicillamine also has the advantage of oral administration, appearing to be adequate treatment for milder cases of lead poisoning.\textsuperscript{xx}

8. Cost-effectiveness

Glogtzer \textit{et al} conducted a cost-effectiveness analysis comparing different strategies for the treatment of childhood lead poisoning. Four treatment options were considered: 1) no treatment (no rx); 2) calcium disodium edetate (EDTA) provocation testing, followed by EDTA chelation if result was positive or no treatment if result is negative (prov); 3) penicillamine chelation with crossover to EDTA provocation testing if toxicity necessitates discontinuation of penicillamine or if there is an unsatisfactory response (pca); 4) EDTA provocation testing followed by EDTA chelation if test result is positive or penicillamine chelation if test result is negative or if there is unsatisfactory response to EDTA (edta).\textsuperscript{xxi}

Outcome measures evaluate included direct medical costs, case of reading disability prevented and quality-adjusted life expectancy (QALE). The QALE is the average projected life expectancy adjusted for long-term disability as well as short-term toxicity and inconvenience associated with medical treatment. It equates the projected lifetime in a state of less than perfect health to the number of equivalent years of perfect health. Cost were obtained from the 1990 rate book of Children’s Hospital, Boston, Massachusetts, United States of America. Future costs and quality-adjusted life years (QALYs) were discounted at 5%.\textsuperscript{xxi}
8.1 Model Assumptions

The model was based on a 2-year old child. It was assumed that each child would receive only one course of treatment. A course of EDTA or penicillamine was considered successful if the blood lead level was reduced to below 25 mcg/dL. It was assumed that a course of penicillamine would successfully reduce the blood lead level 90% of the time; for EDTA a course would be successful 98% of the time. The premise that chelation therapy confers a benefit in neurodevelopment outcomes was a critical assumption in this model. Baseline costs for EDTA assumed outpatient management.

8.2 Results

Baseline results are shown in table 8.1. Both treatment options, EDTA and PCA, result in the same QALE, probability of reading disability, and case of reading disability prevented. The EDTA option has a lower cost per QALY and cost per case prevented compared to no treatment than the PCA option.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($)</th>
<th>QALE (years)</th>
<th>Probability of reading Disability (%)</th>
<th>Case of Reading Disability Prevented Compared with No Rx (%)</th>
<th>Cost/QALY Compared with No Rx ($/year)</th>
<th>Cost/Case Prevented Compared with No Rx ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rx</td>
<td>463</td>
<td>18.25</td>
<td>44.1</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>PROV</td>
<td>786</td>
<td>18.65</td>
<td>35.3</td>
<td>8.8</td>
<td>804</td>
<td>3688</td>
</tr>
<tr>
<td>EDTA</td>
<td>1778</td>
<td>19.27</td>
<td>21.6</td>
<td>22.5</td>
<td>1286</td>
<td>5855</td>
</tr>
<tr>
<td>PCA</td>
<td>2032</td>
<td>19.27</td>
<td>21.6</td>
<td>22.5</td>
<td>1540</td>
<td>6986</td>
</tr>
</tbody>
</table>

*Direct medical costs only, costs of remedial education not included

EDTA dominated PCA in the incremental cost-effectiveness ratios (cost per QALY and cost per case prevented), meaning that PCA is more expensive, but not more effective. Sensitivity analysis was performed for multiple scenarios. When the costs of remedial education were included, EDTA was the preferred treatment option. But, when other direct costs for inpatient EDTA treatment were included, PCA became the preferred treatment option. The authors concluded that initial management with outpatient penicillamine may be the preferred strategy. The authors also concluded that, based on 200,000 children in the United States with blood lead levels > 25 mcg/dL, chelation therapy could prevent more than 45,000 cases of reading disability per year, resulting in savings of $900 million in overall costs.

9. Summary of safety in the treatment of lead poisoning

9.1 Penicillamine

Tertiary references report that penicillamine has been associated with fatalities due to agranulocytosis, aplastic anemia, thrombocytopenia and myasthenia gravis. Proteinuria or hematuria may develop and could be early warning signs of membranous glomerulopathy. Drug fever or skin eruption may develop which usually resolves with temporary discontinuation of the drug.

There were no reports of life threatening adverse events in the reported literature. Reported adverse events included leukopenia, thrombocytopenia, rash, proteinuria, hematuria, elevations in blood-urea-nitrogen, elevations in transaminases, abdominal pain, nausea and vomiting.
Sachs et al reported adverse events for 1001 patients treated with either penicillamine (n= 547) or calcium disodium edetate and penicillamine (n= 454). Several patients reported vomiting or diarrhea, but were able to resume therapy after a brief interruption. Approximately 0.5% of patients developed a pruritic urticaria. Two patients’ symptoms resembled erythema multiforme and erythema annulare and were accompanied by a high fever. A third patient had generalized angioedema without proteinuria. All patients with dermatological reactions responded well to oral antihistamines and withdrawal of penicillamine.xxii

9.2 Calcium disodium edetate

Tertiary references report that calcium disodium edetate has been associated with a lethal increase in intracranial pressure in patients with lead encephalopathy and cerebral edema. Calcium disodium edetate may be nephrotoxic and is not recommended in patients that are anuric, have increasing proteinuria or if hematuria occurs during therapy.vii

There were no reports of life threatening adverse events in the reported literature. Sachs et al reported adverse events for 608 patients that received calcium disodium edetate (n= 154) or calcium disodium edetate and penicillamine (n= 454). There were no significant complications reported. Drowsiness was occasionally noted in the afternoon after the first or second injections. Transient hematuria appearing in one specimen only was observed in six patients. No infections occurred at the injection site.xxii

Three case reports of death from hypocalcemia-induced cardiac arrest were reported in the United States between 2003 and 2005. Two of these patients were children. It is believed that these patients received disodium edetate, rather than calcium disodium edetate. Disodium edetate can be used for the emergency chelation of calcium. The authors recommended that practitioners unfamiliar with chelation therapy consult an expert before undertaking treatment.xxiii

10. Conclusions

There is very little reliable evidence on the efficacy and safety of penicillamine or calcium disodium edetate for the treatment of lead poisoning in children. Much of the available evidence is several years old and not derived from randomized, placebo-controlled trials.

From the evidence identified, however, it appears that calcium disodium edetate is more effective at removing lead, especially for lead induced encephalopathy or when blood lead levels are > 70 mcg/dL. There is no data to support the use of oral penicillamine in lead induced encephalopathy or when blood lead levels are > 70 mcg/dL.

Primary prevention of lead poisoning, including removal of leaded gasoline, and removal of children from lead exposure in their home environment is considered the best treatment for lead poisoning. While blood lead levels <45 mcg/dL are not considered medical emergencies, there are still negative consequences on IQ and cognition at these levels. As an orally available product, penicillamine may have a role in reducing moderate lead poisoning (blood lead levels <45 mcg/dL).

Further studies are needed to determine the goal blood lead level. There are also other oral options that should be assessed for improved safety and efficacy for long-term use compared to penicillamine.
References


7 DRUGDEX® Evaluations. Calcium disodium edetate. 2010.


17 Ruff HA, Bijur PE, Markowitz M, Ma YC, Rosen JF. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA. 1993;269(13):1641-1646


