Chelation Therapy for Childhood Lead Poisoning

The Changing Scene in the 1990s

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Introduction

Recent developments make this a good time to provide an update about chelation therapy for childhood lead (Pb) poisoning. With publication of the revised Centers for Disease Control Pb guidelines,[1] which lower the acceptable blood (B) Pb concentrations, and increased public concern about Pb toxicity, more children are likely to be tested and found to have excessive BPb levels. The availability of a new oral chelating agent approved specifically for children is likely to make pharmacologic therapy more appealing, especially on an outpatient basis.

To date, there is no evidence that chelation therapy prevents or reverses Pb neurotoxicity or that it is superior to removing the child from the Pb source. However, few will disagree that chelation is indicated for BPb levels of 45 μg/dL (2.172 μmol/L) or higher, which is the BPb level consistent with the FDA-approved indication for the oral chelator succimer. These authors, however, agree with a recent recommendation to use 40 μg/dL (1.930 μmol/L) as the lower threshold for chelation therapy because 1) enhanced Pb diuresis (which reverses the biochemical evidence of Pb toxicity and *may* limit or reduce the neurotoxic effects of Pb) was consistently observed in children with BPb levels at or above 40 μg/dL (1.930 μmol/L) after a dose of calcium disodium edetate ($CaNa_2EDTA$),[2] and 2) the 40 μg/dL (1.930 μmol/L) cutoff allows for variability in the laboratory analysis of BPb levels. Also, few disagree that BPb levels below 25 mg/dL (1.206 μmol/L) should *not* receive chelation therapy. The uncertainty lies in the middle; that is, should chelation be used at BPb levels of 25 to 39 (or 44) μg/dL (1.206 to 1.882 [or 2.123] μmol/L)? And, if so, how do we determine which children may benefit and what chelating regimen should be used? Knowledge and practice are evolving and changing rapidly. Definitive answers cannot be given, but the approach presented in this review is based on the pharmacology and clinical studies of the chelating agents, current knowledge of Pb toxicity, and practices at our center as well as at several Pb treatment centers known to us. First, however, the uncertainties and controversies regarding benefits of chelation will be reviewed to avoid any impression that one simply needs a BPb level to decide whether to recommend chelation therapy. After reading this review, perhaps readers will agree with us: Clinicians ought to avoid the murky waters of the chelation controversy and either refer the patient to a Pb treatment center or, at least, consult with a specialist in the treatment of childhood Pb poisoning.

Of all available treatments, the safest and most effective is removing the child from the source of exposure, usually Pb-based paint. Unfortunately, this solution requires political, social, and public-health actions and commitment often beyond the control of clinicians.

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Chelation Considerations in Children with Low-Level Lead Toxicity

The rationale for giving chelating agents to children with Pb poisoning is that the drug will complex with Pb, forming a chelate that can be eliminated in urine, feces, or both. The goals are to reduce the Pb content of target tissues, such as the brain, and to restore normal cellular and tissue function. Although different chelating agents have been shown to increase urine or fecal Pb elimination, reduction of target-tissue Pb content and reversal of toxic effects have *not* been demonstrated in humans. To the contrary, studies in rats indicate that Pb neurotoxicity is not reversible with chelation.[3] Definitive

human studies on reversal or prevention of neurotoxicity are unlikely to be available for some time, but it is encouraging that a placebo-controlled study of chelation intended to provide this information is in the planning stage.

Chelation has long been recognized as relatively inefficient; a course of therapy may remove only 1% to 2% of body Pb content.[4,5] There is also no evidence that available chelating agents have significant access to Pb stored in the brain, the critical target tissue. In fact, a study in rats found that brain Pb content increased following a single dose of $CaNa_2EDTA$.[6] Such findings raise the concern that $CaNa_2EDTA$, and perhaps other chelating agents, redistribute Pb from less- to more-vulnerable body tissues (e.g., bone to brain). Thus, any assumption that risk of neurotoxic effects is decreased when the BPb level is lowered is an untested, albeit appealing, theory. Furthermore, the BPb reduction is likely to be short-lived, or the BPb may rebound to higher than prechelation levels if the child returns to the source of Pb exposure.[7] Concerns about the safety and efficacy of chelation therapy for low-level Pb toxicity underscore the need for primary prevention and early detection, since chelation therapy may be unable to restore patients to their pre-exposure state.

Chelation Therapy for Children with Low-Level Lead Toxicity

There is presently no evidence that chelation therapy will reduce the risk of Pb neurotoxicity. The risk of therapy must be weighed against its theoretical benefit. At BPb levels less than 40 μg/dL (1.930 μmol/L), detection of neurotoxic effects, such as decreased IQ or behavioral changes, is likely to be difficult or impossible, especially since baseline measurements (before exposure to Pb) are usually not available. At BPb levels of 25 to 39 μg/dL (1.206 to 1.882 μmol/L), however, children may show evidence of biochemical toxicity, such as persistently elevated erythrocyte protoporphyrin levels (despite iron replacement), elevated plasma or urine aminolevulinic acid levels, or increased metaphyseal density of the long bones. Such children may have substantial body stores of Pb, as may children with persistently elevated BPb levels despite being removed from the source of Pb exposure. Chelation therapy seems justified in these patients: Benefits of chelation can be followed over several months, along with the BPb levels. Chelation also may be warranted in young children (especially those under 2 years old) because Pb exposure is likely to have been of shorter duration (weeks or months), body burden of Pb may be lower, and body Pb stores may be more accessible to the chelating agent. Also, the immature brain may have greater recuperative potential if the Pb is removed.

Clinical Approach to Chelation Therapy

The decision to begin chelation therapy is not as clear-cut as textbooks may imply, especially for BPb levels between 25 and 40 mg/dL (1.206 to 1.930 μmol/L). Some advise against chelation if a lead mobilization test (LMT) is negative.[2,8,9]

The LMT, also referred to as the "provocative challenge test," has been proposed to identify children with BPb levels of 25 μg/dL (1.206 μmol/L) or higher who are likely to have Pb diuresis with $CaNa_2EDTA$ therapy.[2,8] Currently, there is disagreement regarding the usefulness and interpretation of LMT results,[2,10-13] and a recent informal survey revealed that the LMT was no longer used at half the Pb treatment centers contacted (oral communication, Mary E. O'Connor, M.D., M.P.H., October 1992). In addition, factors other than BPb level have been shown to influence urinary Pb elimination with $CaNa_2EDTA$.[14] Concerns about the safety of a single dose of $CaNa_2EDTA$,[6] the difficulties of obtaining timed urine collections from young children, and recommendations that BPb concentrations above 40 to 45 μg/dL (1.930 to 2.172 μmol/L) warrant chelation therapy are additional reasons that the LMT is controversial. Chisolm's thoughtful reappraisal of the LMT is highly recommended reading.[10]

We do not find the published data supporting the use of the LMT to be compelling. Review of the data indicates that a large percentage of children with BPb levels above 40 to 45 μg/dL would not be "eligible for chelation" based on their LMT results.[8] In our experience, the LMT has produced some unexpected findings, with negative results occurring at BPb levels as high as 74 μg/dL. In addition, the LMT is simply impractical to perform and requires catheterization in young children, which involves risk.

We believe the LMT may be useful in selected patients, but currently its limitations are not fully understood, adequate urine collections are difficult to obtain, and urine flow rates are not standardized.

With current concerns about neurotoxicity at BPb levels as low as 10 μg/dL (0.483 μmol/L) and the availability of succimer for oral outpatient therapy, we needed an alternative to the LMT for decid-

ing which children to chelate. Unsure whether *all* children with BPb concentrations 25 to 40 μg/dL (1.206 to 1.930 μmol/L) should be treated, we reasoned that the subset 1)with biochemical evidence of toxicity, 2) age 2 years or younger, or 3) with persistent BPb elevation more than two or three months after being removed from the Pb exposure source might benefit from chelation. Furthermore, end points of therapy could be defined; namely, reversal of biochemical toxicity or reduction of the BPb level.

Using this rationale to decide which children to chelate, we select the chelating agent based on additional factors. Chelation with succimer is begun if 1) Pb abatement is accomplished or the child can be removed from the source of Pb exposure and 2) compliance with therapy and weekly monitoring visits seems assured. (These two conditions are also mentioned in the succimer package insert.) Another cost-effective, rational approach is to place the child in an alternative, tested, and lead-safe environment, such as temporary housing (including even a hospital ward). Unfortunately, such temporary placement cannot always be provided. When this occurs, $CaNa_2EDTA$ chelation is scheduled on an inpatient basis. Our approach is summarized in Table 1.

For children starting succimer therapy, we obtain a baseline complete blood count (CBC), platelet count, chemistry profile (including transaminase and alkaline phosphatase levels), and BPb levels. Follow-up is weekly for the next three visits, and the same blood tests are done, along with a review of the succimer dosing and queries concerning compliance. Two weeks and one to two months after therapy is completed, the BPb concentration is again determined to evaluate the extent of rebound and the need for additional chelation.

Chelating Agents

British Antilewisite

British antilewisite (BAL) was synthesized in the 1940s as an antidote for lewisite, an arsenical chemical warfare gas. Its use as a Pb chelator was first reported in 1947,[15] although its efficacy was disputed.[16] Reduced mortality in severe childhood Pb encephalopathy after BAL therapy was described in 1950.[5] Current recommendations for use of BAL and other chelating agents can be traced back to Chisolm's extensive review of chelation therapy and clinical observations.[17]

Pharmacology: After intramuscular (IM) administration, the highest concentration of BAL is found in the kidney, followed by the liver and the small intestine.[18] Increased blood concentrations of BAL persist at least two hours after a dose, and within eight hours, about 20% of a dose is recovered as a dithiol in the urine.[19] BAL is also excreted into the feces, and increased fecal Pb excretion has been shown to persist for up to 48 hours after BAL is given,[20] suggesting that the BAL-Pb chelate is excreted into bile or undergoes enterohepatic recycling.

In rat studies, BAL appears more effective than $CaNa_2EDTA$ in reducing bone Pb concentration but less effective in reducing kidney, brain, and soft-tissue Pb content.[20] Whether this is true in humans is unclear, however, because the dosing of Pb and the timing of chelation in the animal studies differed from the human situation.

Indications: Since BAL is water-insoluble, it must be formulated in an oil which is then given by deep IM injection. Dimercaprol is BAL in peanut oil and is the only formulation available for clinical use in the United States. By convention, it will be referred to hereafter as "BAL."

A course of treatment is usually five days. BAL is used in conjunction with $CaNa_2EDTA$ for Pb encephalopathy or when the BPb level is 70 μg/dL (3.378 μmol/L) or higher. BAL is given at a dose of 50 mg/m^2 every four hours in symptomatic patients without encephalopathy. A higher dose is used for Pb encephalopathy (75 mg/m^2 every four hours, not to exceed 450 $mg/m^2/24$ hr). BAL should be given four hours before the first dose of $CaNa_2EDTA$. The BPb level begins to rebound within five to seven days after a course of therapy, and a repeat course of both BAL and $CaNa_2EDTA$ is recommended if the BPb level rebounds above 70 μg/dL (3.378 μmol/L).

Precautions: BAL may precipitate a reaction in children allergic to peanuts. Iron should not be administered during therapy because BAL forms a toxic chelate with iron. Hemolysis may occur in children with glucose-6-phosphate dehydrogenase deficiency.

Toxicity: Intramuscular injection of BAL is very painful. Other relatively common adverse effects include fever, tachycardia, nausea, vomiting, salivation, watery eyes, sweating, and unpleasant breath odor. Convulsions have been reported after doses greater than 5 mg/kg.

Calcium Disodium Edetate

A water-soluble chelating agent, $CaNa_2EDTA$, enhances urinary excretion of Pb, iron, zinc, copper, and other trace metals.[21,22] Fecal Pb excretion is unaffected.[4]

Pharmacology: Human studies in the 1950s showed that approximately 90% of a dose of $CaNa_2EDTA$ appears unmetabo-

Table 1

CLINICAL APPROACH TO CHELATION THERAPY

Condition (usual BPb range: µg/dL)*	Regimen
Encephalopathy (BPb >90-100)	BAL + $CaNa_2EDTA$
Symptomatic, without encephalopathy (BPb 70-90)	
Symptoms possible (BPb 40-69)	

lized in the urine within eight hours following an IM or intravenous (IV) dose.[23] It distributes into a volume roughly equivalent to total body water and does not enter red blood cells. The drug can be detected in cerebrospinal fluid at 5% of the plasma concentration one hour following IV injection. It appears to be eliminated by the kidneys via tubular secretion and glomerular filtration. Because only about 5% of a dose is absorbed from the gastrointestinal (GI) tract, $CaNa_2EDTA$ has not been recommended for oral use. In addition, concerns have been expressed that oral $CaNa_2EDTA$

might increase absorption of Pb present in the GI tract.[1,24]

Indications: High doses of $CaNa_2EDTA$ (1,500 mg/m^2/day) are used in conjunction with BAL therapy for Pb encephalopathy or when the BPb level is 70 μg/dL (3.378 μmol/L) or higher.

The dosage of $CaNa_2EDTA$ is 1,000 mg/m^2/day for BPb levels below 70 μg/dL (3.378 μmol/L). Use of the LMT has been suggested to determine the need for a full course of chelation when the BPb level is 25 to 39, or 44, μg/dL (1.206 to 1.882 [or 2.123] μmol/L); however, there is no consensus regarding the usefulness of this test, and animal studies have raised safety concerns about such testing.[6,10]

The recommendation for twice-daily IV infusion of $CaNa_2EDTA$ is based on the observation in animals that a 6- or 12-hour infusion produced greater urinary Pb excretion than a rapid injection of the same dose.[25,26] Intramuscular injection has been used to minimize fluid administration when children have Pb encephalopathy. In symptomatic children without Pb encephalopathy, a continuous infusion of $CaNa_2EDTA$ is preferred by some clinicians, although a one-hour infusion of each dose is also used. We prefer that the IV dose be given over one hour, followed by a seven-hour fluid infusion.

A course of $CaNa_2EDTA$ is given for five to seven days, with a minimum of two days, and preferably two weeks, between courses. Blood lead levels that rebound to 45 μg/dL (2.172 μmol/L) or higher require additional chelation. Some clinicians repeat courses of therapy until the BPb rebound is less than 30 μg/dL (1.448 μmol/L), which we do as well in selected patients. Since BPb levels rebound and appear to stabilize three to four weeks post-chelation, weekly determination of BPb level may be useful.

Iron deficiency appears to decrease $CaNa_2EDTA$ effectiveness.[14] Replacement iron therapy (4 to 6 mg/kg/day) may be useful prior to chelation therapy in children with low-level Pb toxicity. If chelation is clearly indicated, iron therapy may need to be started after the course of chelation is given.

Precautions: The $CaNa_2EDTA$-Pb chelate is eliminated in urine, so renal function and urine output should be assessed prior to therapy. In severe poisoning, Pb nephropathy can occur, and close monitoring of renal function is imperative during $CaNa_2EDTA$ administration. $CaNa_2EDTA$ should not be used in anuric patients, and careful monitoring is needed in oliguric patients. $CaNa_2EDTA$ may increase lead absorption from the GI tract and should be withheld until GI decontamination is completed if there is evidence of leaded paint (chips) or Pb foreign-body ingestion.[24]

$CaNa_2EDTA$ has a high affinity for zinc and iron. Supplements of either metal should not be given during $CaNa_2EDTA$ therapy because they may decrease the effectiveness of Pb chelation.

Toxicity: Limitation of therapy to a five- to seven-day course is based on the increased risk of nephrotoxicity (hematuria and proteinuria) and mucocutaneous reactions (presumably zinc deficiency) when $CaNa_2EDTA$ is given for longer periods.[27,28] Febrile reactions have also occurred after $CaNa_2EDTA$. Disodium edetate (Na_2EDTA) should never be used because it can produce severe hypocalcemia and cardiac toxicity.

Penicillamine

Penicillamine (PCA) is administered orally and produces an increase in urinary excretion of Pb and other metals. Although not FDA-approved for treatment of Pb poisoning, PCA has been used for outpatient therapy of low-level Pb toxicity, usually in children with persistently elevated BPb levels despite $CaNa_2EDTA$ chelation.[17,29,30] Administration of PCA for about two months, on average, appears effective for lowering BPb levels in children whose levels are 25 to 40 μg/dL (1.206 to 1.930 μmol/L). The high frequency of adverse effects and availability of an alternative, possibly less toxic, oral Pb chelator (i.e., succimer) may reduce the future use of PCA in children.[31]

Pharmacology: In some animal studies, PCA has been shown to mobilize Pb from bone, and in others, depletion of Pb from soft tissues has been observed.[32,33] In animal and in vitro studies, $CaNa_2EDTA$ is a more effective Pb chelator than PCA.[32,34]

In pleasant contrast to other agents, PCA pharmacokinetics has been described in children being treated for low-level Pb toxicity.[35] Oral absorption was erratic, with no relationship between the amount of drug absorbed and changes in BPb levels. The PCA was rapidly eliminated, with an average half-life of 2.9 (± 1.2 SD) hours.

Indications: PCA has been used for outpatient chelation in children with BPb concentrations of 50 μg/dL (2.413 μmol/L) or less, often after one or more courses of parenteral chelation.[17,29,30]

The recommended dose is 30 to 40 mg/kg/day, in three or four divided doses, given two hours before meals. Prolonged treatment has been used to avoid rebound in BPb level. Therapy is continued for 4 to 12 weeks, depending upon BPb levels and adverse drug reactions.

Precautions: PCA should not be used in penicillin-allergic individuals because of cross-reactivity. Food

or ferrous sulfate given after the dose may significantly reduce PCA in blood.[36] Antacids decrease PCA absorption as much as 66%.[36,37] Patient monitoring should include a CBC, urinalysis, and examination for skin rashes.

Toxicity: Nausea and vomiting occur at higher doses of PCA. Hematologic and dermal reactions appear to be immunologic and not dose-related. Reversible leukopenia or mild thrombocytopenia occurred in about 10% of children in one series,[31] but no hematologic abnormalities were noted in other series.[30,38] Eosinophilia may occur in 20% or more of children but may resolve spontaneously. Occasionally, angioedema, urticaria, or maculopapular rash occurs and requires discontinuation of PCA. Proteinuria, microscopic hematuria, and incontinence are infrequent but may resolve with dosage reduction if they do not resolve spontaneously.[31,40]

Succimer

Also known by its chemical acronym DMSA (2,3-dimercaptosuccinic acid), succimer is a water-soluble derivative of BAL. It has a high affinity for Pb, arsenic, and mercury, forming metal complexes that are eliminated in urine. Urinary excretion of iron, zinc, and other essential trace metals is only minimally increased.[41] Succimer is one of the few drugs in the United States approved solely for pediatric use. We feel that succimer is the preferred agent for oral chelation therapy of childhood Pb poisoning.

Succimer is orally administered and appears to be more effective than $CaNa_2EDTA$ or $CaNa_2EDTA$ plus BAL or PCA in producing plumburesis.[42-44] Animal studies indicate that succimer mobilizes Pb from soft tissues, including brain, blood, liver, and kidney; bone lead is inconsistently reduced.[45,46]

Pharmacology: Succimer is incompletely absorbed after an oral dose.[47] It is rapidly biotransformed in plasma and, like $CaNa_2EDTA$, does not enter red blood cells.[48] Because succimer binds extensively (92% to 95%) to plasma proteins, there may be a potential for interactions with other highly protein-bound drugs, such as phenytoin, penicillin or sulfa antibiotics, and nonsteroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen, naproxen). Approximately 89% of urinary succimer is bound to disulfide compounds.[49]

Succimer produces a dose-related decrease in BPb levels and an increase in urine Pb excretion.[43,50] Whether fecal Pb excretion is increased has not been studied. Compared to $CaNa_2EDTA$, succimer appears more effective in restoring normal heme synthesis and reducing brain Pb levels.[44,46] Succimer pharmacology and antidote effectiveness have been reviewed recently.[51]

Indications: Succimer is approved for use in children with BPb concentrations of 45 μg/dL (2.172 μmol/L) and higher who do not have encephalopathy. It has not been studied in Pb encephalopathy, but such patients may be poor candidates for oral chelation because of aspiration risk or reduced or unpredictable drug absorption.

The dosing schedule is regrettably complicated: approximately 10 mg/kg every 8 hours for 5 days, followed by approximately 10 mg/kg every 12 hours for 14 days. This regimen appears sufficient to reduce posttreatment BPb levels to about 70% of the pretreatment value.[43] However, if children remain in the Pb-contaminated environment during therapy or return after treatment, the BPb tends to return to pretreatment levels.[52] It appears that retreatments are often needed to decrease and maintain BPb levels below 25 μg/dL (1.206 μmol/L). The higher the initial BPb level, the more retreatments are likely to be needed.

The use of succimer to treat children with BPb levels of 25 to 45 μg/dL (1.206 to 2.172 μmol/L) is currently under investigation.

Major drawbacks to administering succimer are the fixed-dosage formulation (only 100-mg capsules are available) and the unpleasant taste and "rotten egg" smell of the medication. A similar odor is markedly present in the feces, flatus, and, sometimes, urine of children taking the drug.

Precautions: Although succimer does not increase GI absorption of Pb in rats, it is unwise to assume the same is true in humans, because the drug has different absorption patterns across species.[51,53] Until this issue is resolved, children should not receive succimer unless they are removed from the source of Pb poisoning.

Toxicity: In clinical use, reported toxicity is minimal to date. Transient elevation of serum glutamic-pyruvate transaminase was observed in adults but not in children.[54] Reported adverse effects in children include nausea, vomiting, diarrhea, loose stools, appetite loss, and foul-smelling urine and/or stools.[47] In approximately 40 children we have treated, two noteworthy drug-related events occurred. One child developed an anaphylactoid reaction within three days of starting a second course of succimer. Two children experienced a dramatic increase in serum alkaline phosphatase (bone fraction) during therapy, which continued to rise after therapy ended and returned to normal by five weeks posttherapy. No evidence was found of bone disease or abnormality.

Conclusion

Chelation therapy for childhood Pb poisoning is an evolving field undergoing careful reconsideration, and many unanswered questions remain. Uncertainty and controversy characterize questions about which children with low-level Pb poisoning are candidates for chelation therapy and which drug regimen is best. Although our approach is summarized (Table 1), primary-care practitioners are advised to refer these patients or consult with a Pb treatment clinic for current recommendations.

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