Treatment Guidelines for Lead Exposure in Children

Committee on Drugs

The recent introduction of an effective oral chelating agent for the reduction of a body burden of lead and the changing standards of care for children exposed to lead prompted the Committee on Drugs to review the therapy for lead intoxication. This statement reviews the pharmacology of available chelating agents. Screening standards and detailed discussions of environmental control and nutritional management have been previously published by the American Academy of Pediatrics.[1]

Lead intoxication has been a problem throughout history. In the early 1940s it was recognized that the amount of lead in the urban industrial environment had increased to the point at which a striking number of children demonstrated hematologic effects and clinical signs of acute lead intoxication. Blood lead levels in children in the United States on average have decreased, and rarely are children seen with blood lead levels of greater than 70 μg/dL. Even in patients with levels of greater than 50 μg/dL, "classic" laboratory and clinical findings of lead toxicity, such as basophilic stippling and encephalopathy, are rarely seen.[2] In the past, therapy was based on the ability of chelators to reverse the hematologic effects of lead and halt the progression of lead encephalopathy. The efficacy of chelation therapy for children without the hematologic or neurologic findings has yet to be demonstrated; a decrease in blood lead concentration is the only discernible goal for chelation therapy in this setting. Eliminating the source of lead exposure also can accomplish this result. A recent study of moderately lead-exposed children receiving chelation therapy failed to demonstrate any additional benefit of $CaNa_2$-ethylenediaminetetraacetic acid (EDTA) compared with abatement at improving cognitive function.[3]

Our understanding of the pharmacokinetics of lead and its alteration by chelating agents is rudimentary. Human lead pharmacokinetics has been studied in small series.[4] Isotopic lead administered at low doses in adult human subjects revealed that lead has an extremely long terminal elimination half-life in blood of more than 30 days and similarly long rates of uptake into tissue. Rates of elimination from bone were so long that they could not be determined but are estimated in years. It is therefore extremely difficult to estimate the total body burden of lead on the basis of blood lead concentrations. In the face of increases in lead intake, the blood concentration may be artificially elevated until equilibration occurs. Similarly, drug therapy that removes lead primarily from the blood or soft tissue may have a limited impact on the total body burden but may lower the blood lead concentration until deeply stored lead reequilibrates into the circulation. It may be predicted, then, that chelation of chronically lead-exposed individuals would be followed by significant reequilibration and that long-term therapy may be necessary to assure that total body burden has been reduced despite falling serum concentrations of lead.

Concerns about the safety of chelation have focused on experimental evidence from animals that chelating agents may cause lead distribution into certain body tissues, particularly the brain.[5] These results may not apply to children, who typically have chronic, low-level exposure. The long-term outcome after treatment with succimer is the subject of an ongoing multicenter study sponsored by the National Institute of Environmental Health Sciences.

CHELATING AGENTS

There are currently two parenteral and two oral agents used for the chelation of lead. They act by mobilizing lead from various sites in the body. Effective use of these agents requires an understanding of their pharmacology and toxicology.

Dimercaprol (BAL in Oil)

Dimercaprol was first developed as an antidote for Lewisite (an arsenical chemical weapon) and is useful in a variety of metal intoxications, including lead. The acronym BAL is based on the name "British antilewisite." Dimercaprol is also referred to as dimercaptopropanol. BAL is a polar compound that forms a nonpolar 2:1 chelate with lead, which is excreted in bile and urine.

Almost 50% of patients experience side effects when treated with dimercaprol at the doses commonly used.[6] Many of the side effects are related to histamine release and can be blunted by the concurrent use of antihistamines. In addition, fever is commonly described in children. Despite the high incidence of side effects, dimercaprol has remained in use for more serious lead intoxication because of concerns that $CaNa_2$EDTA therapy may translocate lead into the central nervous system and increase the potential for encephalopathy. Pretreatment of seriously exposed patients with BAL traditionally has been recommended to avoid precipitation of lead

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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encephalopathy. Data also have shown a more rapid decline in blood lead concentration during chelation when BAL was added to $CaNa_2EDTA$.[7] Because the impact of chelation on the total body burden as measured by postchelation lead levels may be the more important determinant of efficacy, the rate of change in the blood lead concentration may be irrelevant. The rationale for the use of BAL with $CaNa_2EDTA$ in the seriously intoxicated, lead-exposed patient without encephalopathy recently has been challenged on this basis.[8] The addition of BAL to $CaNa_2EDTA$ therapy increased the incidence of serum hepatic enzyme elevation and vomiting without resulting in appreciable differences in postchelation blood lead concentrations. Because the incidence of encephalopathy is generally low, a very large series would be needed to demonstrate the safety of this approach. The high mortality and morbidity from encephalopathy, however, necessitates that $CaNa_2EDTA$ be used with BAL in severe intoxications (blood lead levels >70 μg/dL).

Significant intravascular hemolysis has been reported with BAL therapy in two patients deficient in glucose-6-phosphate dehydrogenase.[9] High-risk populations should be screened for this deficiency before therapy, and susceptible individuals should be monitored for hemolysis during treatment. Patient sensitivity to peanuts contraindicates the use of BAL, because it is prepared in a peanut oil solution.

The recommended doses of BAL for children are empiric. Doses have been recommended based on both milligrams per kilogram of body weight and milligrams per square meter. The toxicity of this drug and the currently available alternatives now mandate its use in only the most serious cases of lead intoxication (blood lead levels >70 μg/dL). Given the intrinsic toxicity of BAL and its use only in populations with high lead concentrations at some risk for encephalopathy, inpatient administration is necessary with close cardiovascular and mental status monitoring. Routine pretreatment with diphenhydramine is recommended. Unfortunately, BAL can only be given intramuscularly because of its solubility characteristics. Also, iron supplementation is not recommended during treatment, because BAL may form a complex with iron that results in toxicity.[10] The scientific basis for this recommendation is limited to a study of BAL therapy for acute iron poisoning in mice and may have limited relevance to therapeutic iron supplementation in chronic lead exposure.[11] Some sources recommend alkalinization of the urine to keep the BAL-lead complex from dissociating.

Calcium Disodium EDTA

Ethylenediaminetetraacetic acid is the chemical name for the compound more popularly known as EDTA. This compound is also referred to in the literature as "edetate" and can be found in a variety of cation combinations, including calcium, sodium, and zinc. The ability of this compound to form various high-affinity salts has made it useful as a chelating agent for a variety of metal intoxications. In the United States, the clinically recommended form is the calcium disodium salt of EDTA, referred to as calcium disodium edetate (calcium disodium versenate), or $CaNa_2EDTA$, which is the term used in this guideline. Disodium edetate (sodium EDTA) should not be confused with calcium disodium edetate ($CaNa_2EDTA$); the use of the former may result in severe hypocalcemia and possible death.

$CaNa_2EDTA$ has a high affinity for lead. This compound and dimercaprol have constituted the backbone for the treatment of lead intoxication for many years. The very low bioavailability (<5%) of $CaNa_2EDTA$ from oral intake, however, necessitates hospitalization and parenteral administration for effective treatment.

In general, $CaNa_2EDTA$ has been demonstrated to decrease blood lead concentrations, to reverse the hematologic effects of lead, and to increase the excretion of lead in urine. One large series reported 1155 patients treated with $CaNa_2EDTA$ alone or in combination with penicillamine[12]; unfortunately, no indicators of neurologic outcome were measured. The investigators described a decreased incidence of encephalopathy during the period when treatments were initiated.

The effects of treatment with either $CaNa_2EDTA$ or BAL on the outcome of lead encephalopathy have been examined in a small series.[13] No difference in outcome was demonstrated. Similarly, an animal model[14] was unable to demonstrate the benefits of $CaNa_2EDTA$ in treating neurotoxicity; in fact, the findings suggested that neurotoxicity may have increased. To add to the confusion, 47 children with the initial lead levels of greater than 50 μg/dL were assessed after treatment with $CaNa_2EDTA$ for differences in intellectual performance compared with a sibling control group.[15] No differences were found. The comparability of these groups is questionable, however, because no pretreatment data were presented. A recent study did not demonstrate any additional benefit of $CaNa_2EDTA$ therapy compared with abatement in improving performance on tests of cognitive functioning as blood lead levels decreased.[3] The relevance of this study is limited because there was no control group, because of the impact of iron supplementation, and because it was possible that repeated exposure to the testing procedure caused the improvement.

The use of $CaNa_2EDTA$ as a sole agent for treatment of patients at risk for encephalopathy is of concern because of the possibility of lead redistribution from soft tissues to the central nervous system. Some support for this concern has come from an animal model demonstrating an increase in levels of lead in brain tissue after treatment with $CaNa_2EDTA$.[16] Case reports of fatal lead encephalopathy associated with $CaNa_2EDTA$ treatment are consistent with the evidence from animal studies.[17] Although one case report has described the effective treatment of lead encephalopathy with $CaNa_2EDTA$,[18] it is not recommended as the sole agent for therapy in patients with blood lead levels of greater than 70 μg/dL or with signs and symptoms of encephalopathy.

The appropriate protocol for administration of

$CaNa_2EDTA$ is controversial. The intramuscular injection of $CaNa_2EDTA$ is extremely painful and generally is administered in a mixture with procaine to decrease the pain. Rapid intravenous administration may produce severe local and systemic side effects. Concerns regarding precipitation of acute encephalopathy have resulted in a warning against intravenous administration from the Food and Drug Administration as part of the package label. Intravenous administration in patients who are not at high risk for encephalopathy seems to be safe if the $CaNa_2EDTA$ is infused slowly during a controlled period, such as 4 hours, in a diluted (<0.5%) solution to avoid phlebitis. No controlled data exist, however, on the relative safety and efficacy of $CaNa_2EDTA$ at varied rates of drug delivery. Recommendations range from 20 minutes[10] to a 24-hour continuous infusion of $CaNa_2EDTA$. It would seem prudent to err on the side of the slowest rate of administration that is clinically feasible.

The toxicity of $CaNa_2EDTA$ is difficult to quantify. Many of the signs and symptoms of toxicity associated with this drug were described shortly after its introduction in adult patients receiving relatively high doses. The kidney is one major site of $CaNa_2EDTA$ toxicity in these studies and in animal studies. Lead itself is associated with nephropathy in chronic exposure, although the incidence in children seems to be lower than that described in the literature for occupational exposures. In a series of 130 children treated for lead intoxication with a combination of dimercaprol and $CaNa_2EDTA$, signs of nephrotoxicity developed in 13%, and 3% experienced acute renal failure.[19] Acute renal failure was manifest as oliguria for 2 to 4 days and was treated without dialysis, with renal function gradually returning to normal. In a study comparing intramuscular to intravenous $CaNa_2EDTA$ therapy in 90 children, both routes were associated with proteinuria and increasing levels of serum urea nitrogen in greater than 25% of the patients.[20] A single case report described the effectiveness of intraperitoneal $CaNa_2EDTA$ therapy in patients with renal failure requiring chelation therapy.[21] Appropriate fluid therapy and monitoring of urine output and renal function are essential with the use of $CaNa_2EDTA$.

It is apparent that the incidence of side effects from $CaNa_2EDTA$ has decreased in association with the use of the calcium salt, better infusion techniques, intervention at lower blood lead levels, and lower doses. Symptoms described in older series include headache, fever, chills, malaise, thirst, nausea and vomiting, and urinary tract symptoms. The high incidence of cardiovascular instability described in older series was likely the result of using sodium EDTA and resultant hypocalcemia.

Chronic toxicity may be related to the ability of $CaNa_2EDTA$ to increase the excretion of cations such as zinc, resulting in zinc deficiency during prolonged treatment. Salts using zinc as a cation are effective in the treatment of lead intoxication.[22] It is unlikely, however, that such a preparation will become available in the United States. Additional evidence suggests that it may be safe to administer zinc while using $CaNa_2EDTA$ to obviate the effects of long-term chelation therapy, although this may decrease the effectiveness of therapy and is unlikely to be needed for routine treatment.[23]

The significant incidence of adverse reactions associated with chelation using $CaNa_2EDTA$ mandates careful patient monitoring and follow-up. Indicators of renal and hepatic function should be followed up at regular intervals.

The EDTA Mobilization (Challenge) Test

Various $CaNa_2EDTA$ mobilization tests have been suggested as indicators of response to chelation therapy. The lack of measurable end points of chelation therapy in children with relatively low-level exposures to lead and the toxicity of $CaNa_2EDTA$ make these tests obsolete. In addition, the use of the challenge test is fraught with technical difficulties.[24,25] Weinberger et al[26] performed 248 $CaNa_2EDTA$ mobilization tests and found that the test was not a consistent predictor of the body burden of lead, although it did demonstrate that higher blood lead levels were associated with higher levels of lead excretion during the treatment period. Not surprisingly, blood lead levels are significantly correlated with the amount of lead excreted in response to a dose of $CaNa_2EDTA$.[27] The difficulty and expense of performing $CaNa_2EDTA$ challenge tests and the potential for increasing lead toxicity by using $CaNa_2EDTA$ alone make this testing obsolete.

Succimer

Succimer is a water-soluble analog of dimercaprol, which is also known as 2,3-meso-dimercaptosuccinic acid, or DMSA. The molecular differences from dimercaprol give succimer the advantage of oral administration. In addition, it is relatively specific for heavy metals in vitro and only minimally enhances the excretion of iron, zinc, and calcium in small series studied clinically.

Experience with succimer in the United States is relatively limited. Graziano et al[28] studied a group of children with blood lead concentrations of 31 to 49 μg/dL. These children randomly received either one of three incremental doses of succimer or $CaNa_2EDTA$. Succimer increased the excretion of lead in the urine in a dose-dependent fashion. Oral administration of succimer at the highest of the three doses increased lead excretion to a greater degree than intravenous $CaNa_2EDTA$ therapy. This study also measured a functional indicator of hemoglobin synthesis, aminolevulinic acid dehydratase activity, which was increased toward normal in response to the administration of succimer at the highest dose.

Findings from animal studies suggest that succimer is not likely to precipitate encephalopathy in human patients, in contrast to $CaNa_2EDTA$, although clinical experience in high-risk patients is not extensive.[29] Three adults with lead-induced encephalopathy demonstrated clinical improvement when treated with succimer.[30]

Adverse reactions to succimer in a series of 191 patients reported to the manufacturer included mild gastrointestinal symptoms in 12% of children, gen-

eral malaise in 5%, and transient elevation of liver enzymes in 4%.[31] In a smaller series, a decrease in hemoglobin level was reported in 12 of 41 children during succimer therapy, although the cause was not determined.[32] Hypersensitivity reactions have been reported, including chills and fever, urticaria, and rash. The manufacturer has reported a small number of patients with reversible neutropenia during therapy with succimer (package insert). The potential for anemia and neutropenia mandates ongoing surveillance of hematologic parameters during therapy. Long-term evaluation of large numbers of patients is necessary to discover the incidence of rare, but potentially more serious, side effects. Similarly, no data on toxicity are available to compare the incidence of side effects between available chelating agents at this time. The toxic interaction with iron reported for dimercaprol has not been reported for succimer.[33] However, oral combination therapy is not recommended until studies on the efficacy of this approach are obtained. Unlike dimercaprol, succimer has not caused hemolysis in a small number of patients with glucose-6-phosphate dehydrogenase deficiency receiving chelation therapy.[31]

In serious lead intoxication, the issue of outpatient compliance to an oral medication should be considered before deciding on therapy. It has been suggested that $CaNa_2EDTA$ be used for patients who may be noncompliant. Patients also may be hospitalized to undergo oral succimer treatment to ensure compliance rather than use a more toxic agent by the parenteral route.

The major question that remains regarding the role of succimer seems to be the indications for its use in patients with blood lead levels in the range of 25 to 45 μg/dL. Succimer, although approved by the Food and Drug Administration, is not currently labeled for treatment of patients with blood lead levels in this range but has been shown to lower the body burden of lead. The ease with which succimer can be used on an outpatient basis makes it tempting for practitioners to prescribe. Given the lack of data regarding an improvement in outcome associated with any chelation therapy and the lack of sufficient data on safety to exclude rare but potentially severe side effects, therapy for lower-level exposures should include only environmental and nutritional intervention. It is hoped that this issue can be resolved in the near future; the American Academy of Pediatrics strongly endorses participation in current research protocols on the treatment of low-level lead exposure and avoidance of routine chelation therapy.

D-Penicillamine

Penicillamine (D-dimethyl cysteine) also offers an alternative in the oral treatment of lead poisoning, although it is not currently labeled for use in the treatment of lead poisoning. This drug was originally found in the urine of patients with Wilson's disease and was noted to bind to various metals.[34] In animal studies, lead in bone seems to be more effectively mobilized by penicillamine than lead in soft tissues.[5,35] However, $CaNa_2EDTA$ seems to be a more effective lead chelator than penicillamine in animals and tissue culture.[5,36] Questions have been raised about the safety of using either agent for low-level lead toxicity, because animal studies have demonstrated that lead may redistribute into soft tissues after penicillamine or $CaNa_2EDTA$ therapy.[5,6]

The clinical efficacy of penicillamine was described by Sachs et al[12] and Vitale et al.[37] In contrast, Marcus[38] reported minimal efficacy. Because the doses administered in these reports were similar, continued lead exposure most likely explains the less dramatic decline in blood lead levels in the latter study. In a single study, when children were removed from further exposure and treated with penicillamine, the decline in blood lead levels and the reversal of hematologic toxicity were more rapid than the decline in toxicity resulting solely from eliminating the source of lead exposure.[39]

The toxicity of pencillamine has been described based on its use for several indications in both adults and children. Toxicity of the racemic mixture used to treat chronic arthritis in adults may account for the severity of some of these symptoms. In children, nausea and vomiting appear more often at doses exceeding 60 mg/kg per day and may respond to a decrease in dosage.[12] Adverse hematologic and dermal effects seem to be hypersensitivity reactions and are not dose related. Reversible leukopenia or mild thrombocytopenia occurred in about 10% of children in one study,[40] but no hematologic abnormalities were noted at similar dosages in two other series.[39,41] Eosinophilia (defined as >18% eosinophils) has been noted in 20% or more of treated children.[37,38] About 0.5% to 1% of children may develop angioedema, urticaria, or maculopapular eruptions that necessitate discontinuation of drug therapy.[12,39] Less commonly reported reactions are proteinuria, microscopic hematuria, and urinary incontinence.[12,40]

Food or ferrous sulfate may reduce the level of penicillamine in blood by 35% or more.[42] Antacids decrease penicillamine absorption by as much as 66%.[42,43]

The recommended dose and duration of therapy with penicillamine have been empirically derived. Doses have ranged from 100 mg/kg per day (in earlier studies) to 20 to 30 mg/kg per day (more recently). The duration of therapy is typically 4 to 12 weeks, depending on the pretreatment blood lead concentration. Often, these children have had prior chelation with $CaNa_2EDTA$ and/or BAL, and the goal of oral chelation therapy is to reduce the body burden so the blood lead does not rebound to unacceptable levels.[39,40] The overall toxicity profile of penicillamine relegates it to a third-line agent, indicated only when unacceptable reactions have occurred to succimer and $CaNa_2EDTA$ and continued therapy is considered important.

TREATMENT RECOMMENDATIONS BASED ON CONFIRMED BLOOD LEAD RESULTS

Venous blood samples should be used to determine treatment.

1. Chelation treatment is not indicated in patients with blood lead levels of less than 25 μg/dL,

although environmental intervention should occur.

2. Patients with blood lead levels of 25 to 45 μg/dL need aggressive environmental intervention but should not routinely receive chelation therapy, because no evidence exists that chelation avoids or reverses neurotoxicity. If blood lead levels persist in this range despite repeated environmental study and abatement, some patients may benefit from (oral) chelation therapy by enhanced lead excretion.
3. Chelation therapy is indicated in patients with blood lead levels between 45 and 70 μg/dL. In the absence of clinical symptoms suggesting encephalopathy (eg, obtundation, headache, and persistent vomiting), patients may be treated with succimer at 30 mg/kg per day for 5 days, followed by 20 mg/kg per day for 14 days. Children may need to be hospitalized for the initiation of therapy to monitor for adverse effects and institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use $CaNa_2EDTA$ as inpatient therapy at 25 mg/kg per day for 5 days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.
4. Patients with blood levels of greater than 70 μg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available. Lead encephalopathy is a life-threatening emergency that should be treated using contemporary standards for intensive care treatment of increased intracranial pressure, including appropriate pressure monitoring, osmotic therapy, and drug therapy in addition to chelation therapy. Therapy is initiated with intramuscular dimercaprol (BAL) at 25 mg/kg per day divided into six doses. The second dose of BAL is given 4 hours later, followed immediately by intravenous $CaNa_2EDTA$ at 50 mg/kg per day as a single dose infused during several hours or as a continuous infusion. Current labeling of $CaNa_2EDTA$ does not support the intravenous route of administration, but clinical experience suggests that it is safe and more appropriate in the pediatric population.[10,20,28] The hemodynamic stability of these patients, as well as changes in neurologic status that may herald encephalopathy, needs to be closely monitored. Adequate hydration should be maintained to ensure renal excretion.

Therapy needs to be continued for a minimum of 72 hours. After this initial treatment, two alternatives are possible: (1) the parenteral therapy with two drugs ($CaNa_2EDTA$ and BAL) may be continued for a total of 5 days; or (2) therapy with $CaNa_2EDTA$ alone may be continued for a total of 5 days. If BAL and $CaNa_2EDTA$ are used for the full 5 days, a minimum of 2 days with no treatment should elapse before considering another 5-day course of treatment. In patients with lead encephalopathy, parenteral chelation should be continued with both drugs until they are clinically stable before therapy is changed.

Follow-Up

After chelation therapy, a period of reequilibration of 10 to 14 days should be allowed, and another blood lead concentration should be obtained. Subsequent treatment should be based on this determination, following the categories presented above.

It is not our intent in this review to neglect issues of abatement of housing, remediating unusual exposures, nutrition, and screening for exposure. These issues are discussed elsewhere[1] and mandate equal consideration in treating the patient exposed to lead.

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