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 CaNa2-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 CaNa2-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
encephalopathy. Data also have shown a more rapid
decline in blood lead concentration during chelation
when BAL was added to CaNa₂EDTA. 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 irrel-
levant. The rationale for the use of BAL with
CaNa₂EDTA in the seriously intoxicated, lead-ex-
posed patient without encephalopathy recently has
been challenged on this basis.8 The addition of BAL
to CaNa₂EDTA therapy increased the incidence of
serum hepatic enzyme elevation and vomiting with-
out resulting in appreciable differences in postchel-
tation blood lead concentrations. Because the incidence
of encephalopathy is generally low, a very large se-
ries would be needed to demonstrate the safety of
this approach. The high mortality and morbidity
from encephalopathy, however, necessitates that
CaNa₂EDTA be used with BAL in severe intoxica-
tions (blood lead levels >70 μg/dL).

Significant intravascular hemolysis has been re-
ported 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. Pa-
tient 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 popula-
tions with high lead concentrations at some risk for
encephalopathy, inpatient administration is neces-
sary with close cardiovascular and mental status
monitoring. Routine pretreatment with diphenyl-
dramine is recommended. Unfortunately, BAL can
only be given intramuscularly because of its solubil-
ity 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 lim-
ited to a study of BAL therapy for acute iron poison-
ing in mice and may have limited relevance to ther-
apeutic 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 var-
iou high-affinity salts has made it useful as a che-
lating 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 versen-
ate), or CaNa₂EDTA, which is the term used in this
guide. Disodium edetate (sodium EDTA) should
not be confused with calcium disodium edetate
(CaNa₂EDTA); the use of the former may result in
severe hypocalcemia and possible death.

CaNa₂EDTA has a high affinity for lead. This com-
pound and dimercaprol have constituted the back-
bone for the treatment of lead intoxication for many
years. The very low bioavailability (<5%) of
CaNa₂EDTA from oral intake, however, necessitates
hospitalization and parenteral administration for ef-
fective treatment.

In general, CaNa₂EDTA has been demonstrated to
decrease blood lead concentrations, to reverse the
hematologic effects of lead, and to increase the ex-
cretion of lead in urine. One large series reported
1155 patients treated with CaNa₂EDTA alone or in
combination with penicillamine12; 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 CaNa₂EDTA 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
model14 was unable to demonstrate the benefits of
CaNa₂EDTA in treating neurotoxicity; in fact, the
findings suggested that neurotoxicity may have in-
creased. To add to the confusion, 47 children with
the initial lead levels of greater than 50 μg/dL were
assessed after treatment with CaNa₂EDTA for differ-
ces 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 pre-
sented. A recent study did not demonstrate any ad-
ditional benefit of CaNa₂EDTA therapy compared
with abatement in improving performance on tests of
cognitive functioning as blood lead levels decreased.13
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 CaNa₂EDTA as a sole agent for treat-
ment of patients at risk for encephalopathy is of
concern because of the possibility of lead redistri-
bution from soft tissues to the central nervous sys-
tem. Some support for this concern has come from
an animal model demonstrating an increase in
levels of lead in brain tissue after treatment
with CaNa₂EDTA.16 Case reports of fatal lead en-
cephalopathy associated with CaNa₂EDTA treatment
are consistent with the evidence from animal stud-
ies.17 Although one case report has described the
effective treatment of lead encephalopathy with
CaNa₂EDTA,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
CaNa₂EDTA is controversial. The intramuscular injection of CaNa₂EDTA 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 CaNa₂EDTA 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 CaNa₂EDTA at varied rates of drug delivery. Recommendations range from 20 minutes to a 24-hour continuous infusion of CaNa₂EDTA. It would seem prudent to err on the side of the slowest rate of administration that is clinically feasible.

The toxicity of CaNa₂EDTA 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 CaNa₂EDTA 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 CaNa₂EDTA, signs of nephrotoxicity developed in 13%, and 3% experienced acute renal failure. 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 CaNa₂EDTA therapy in 90 children, both routes were associated with proteinuria and increasing levels of serum urea nitrogen in greater than 25% of the patients. A single case report described the effectiveness of intraperitoneal CaNa₂EDTA therapy in patients with renal failure requiring chelation therapy. Appropriate fluid therapy and monitoring of urine output and renal function are essential with the use of CaNa₂EDTA.

It is apparent that the incidence of side effects from CaNa₂EDTA 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 CaNa₂EDTA 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. 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 CaNa₂EDTA 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.

The significant incidence of adverse reactions associated with chelation using CaNa₂EDTA 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 CaNa₂EDTA 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 CaNa₂EDTA make these tests obsolete. In addition, the use of the challenge test is fraught with technical difficulties. Weinberger et al performed 248 CaNa₂EDTA 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 CaNa₂EDTA. The difficulty and expense of performing CaNa₂EDTA challenge tests and the potential for increasing lead toxicity by using CaNa₂EDTA 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 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 CaNa₂EDTA. 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 CaNa₂EDTA 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 CaNa₂EDTA, although clinical experience in high-risk patients is not extensive. Three adults with lead-induced encephalopathy demonstrated clinical improvement when treated with succimer.

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%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 re-
caus[...]

TREATMENT RECOMMENDATIONS BASED ON CONFERMED 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 CaNa₂EDTA 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 CaNa₂EDTA at 50 mg/kg per day as a single dose infused during several hours or as a continuous infusion. Current labeling of CaNa₂EDTA does not support the intravenous route of administration, but clinical experience suggests that it is safe and more appropriate in the pediatric population. 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 (CaNa₂EDTA and BAL) may be continued for a total of 5 days; or (2) therapy with CaNa₂EDTA alone may be continued for a total of 5 days. If BAL and CaNa₂EDTA 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 and mandate equal consideration in treating the patient exposed to lead.

Treatment Guidelines for Lead Exposure in Children
Committee on Drugs
*Pediatrics* 1995;96;155

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/96/1/155