



Weekly

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Deaths Associated with Hypocalcemia from Chelation Therapy --- Texas, Pennsylvania, and Oregon, 2003--2005

Chelating agents bind lead in soft tissues and are used in the treatment of lead poisoning to enhance urinary and biliary excretion of lead, thus decreasing total lead levels in the body (*1*). During the past 30 years, environmental and dietary exposures to lead have decreased substantially, resulting in a considerable decrease in population blood lead levels (BLLs) (*2*) and a corresponding decrease in the number of patients requiring chelation therapy. Chelating agents also increase excretion of other heavy metals and minerals, such as zinc and, in certain cases, calcium (*1*). This report describes three deaths associated with chelation-therapy--related hypocalcemia that resulted in cardiac arrest. Several drugs are used in the treatment of lead poisoning, including edetate disodium calcium (CaEDTA), dimercaperol (British anti-Lewisite), D-penicillamine, and meso-2,3-dimercaptosuccinic acid (succimer). Health-care providers who are unfamiliar with chelating agents and are considering this treatment for lead poisoning should consult an expert in the chemotherapy of lead poisoning. Hospital pharmacies should evaluate whether continued stocking of Na₂EDTA is necessary, given the established risk for hypocalcemia, the availability of less toxic alternatives, and an ongoing safety review by the Food and Drug Administration (FDA). Health-care providers and pharmacists should ensure that Na₂EDTA is not administered to children during chelation therapy.

Chelating agents, especially those intended for use in children, should be effective in reducing lead and other heavy metals from the body without producing substantial adverse effects on levels of critical serum electrolytes, such as calcium. The only agent recommended for intravenous (IV) chelation therapy for children is CaEDTA (*1*). However, hospital formularies usually stock multiple chelation agents. One such agent, Na₂EDTA, was formerly used for treatment of hypercalcemia, but its use has become infrequent because of concerns regarding nephrotoxicity and because of the availability of less toxic alternatives (*3*). Furthermore, Na₂EDTA contains a warning stating, "The use of this drug in any particular patient is recommended only when the severity of the clinical condition justifies the aggressive measures associated with this type of therapy." According to the package insert, Na₂EDTA is "indicated in selected patients for the emergency treatment of hypercalcemia and for the control of ventricular arrhythmias associated with digitalis toxicity." According to FDA and CDC, the safety and effectiveness of Na₂EDTA in pediatric patients has not been established, and its use is not recommended because it induces hypocalcemia and possibly fatal tetany (*1*).

In 2005, the Texas Department of Health childhood lead poisoning surveillance program reported a death attributable to chelation-associated hypocalcemia to CDC. Subsequently, CDC queried state and local lead-surveillance programs regarding chelation-related fatalities; additional deaths were identified in Pennsylvania and Oregon.

Case Reports

Texas. In February 2005, a girl aged 2 years who was tested for blood lead during routine health surveillance had a capillary BLL of 47 $\mu\text{g/dL}$. A venous BLL of 48 $\mu\text{g/dL}$ obtained 12 days later confirmed the elevated BLL. A complete blood count and iron study conducted concurrently revealed low serum iron levels and borderline anemia. On February 28, 2005, the girl was admitted to a local medical center for combined oral and IV chelation therapy.

The patient's blood electrolytes at admission were within normal limits. Initial medication orders included IV Na_2EDTA and oral succimer (an agent primarily used for treatment of lead poisoning). The medication order subsequently was corrected by the pediatric resident to IV CaEDTA . At 4:00 p.m. on the day of admission, the patient received her first dose of IV CaEDTA (300 mg in 100 mL normal saline at 25 mL/hr). At 4:35 p.m., she was administered 200 mg of oral succimer. Her vital signs remained normal throughout the night. At 4:00 a.m. the next day, a dose of IV Na_2EDTA (instead of IV CaEDTA) was administered. An hour later, the patient's serum calcium had decreased to 5.2 mg/dL (normal value for pediatric patients: 8.5--10.5 mg/dL). At 7:05 a.m., the child's mother noticed that the child was limp and not breathing. Bedside procedures did not restore a normal cardiac rhythm, and a cardiac resuscitation code was called at 7:25 a.m. The child had no palpable pulse or audible heartbeat. Repeat laboratory values for serum drawn at 7:55 a.m. indicated that the serum calcium level was <5.0 mg/dL despite repeated doses of calcium chloride. All attempts at resuscitation failed, and the girl was pronounced dead at 8:12 a.m.

An autopsy revealed no results of toxicologic significance. A postmortem radiologic bone survey indicated areas of sclerosis at the metaphyses (growth arrest and recovery lines compatible with lead exposure). The cause of death was recorded as sudden cardiac arrest resulting from hypocalcemia associated with chelation therapy. The hospital's child mortality review board findings indicated that a dose of IV Na_2EDTA was unintentionally administered to the child.

Pennsylvania. In August 2005, a boy aged 5 years with autism died while receiving IV chelation therapy with Na_2EDTA in a physician's office. During the chelation procedure, the mother noted that the child was limp. The physician initiated resuscitation, and an emergency services team transported the child to the hospital. At the emergency department (ED), further resuscitation was attempted, including administration of at least 1 and possibly 2 doses of IV calcium chloride. Subsequently, the boy's blood calcium level was recorded in the ED as 6.9 mg/dL. The child did not regain consciousness. The coroner examination indicated cause of death as diffuse, acute cerebral hypoxic-ischemic injury, secondary to diffuse subendocardial necrosis. The myocardial necrosis resulted from hypocalcemia associated with administration of Na_2EDTA . The case is under investigation by the Pennsylvania State Board of Medicine.

Oregon. In August 2003, a woman aged 53 years with no evidence of coronary artery disease, intracranial disease, or injury was treated with 700 mg IV EDTA in a naturopathic practitioner's clinic. The EDTA was provided by a compounding laboratory (Creative Compounding, Wilsonville, Oregon) and was administered by the practitioner to remove heavy metals from the body. The practitioner had provided a similar treatment to the patient on three previous occasions, once in June 2003 and twice in July 2003. Approximately 10--15 minutes after treatment began, the patient became unconscious. Cardiopulmonary resuscitation was initiated, and an emergency services team was contacted. Attempts to revive the patient en route to and in the ED were unsuccessful. The medical examiner determined the cause of death to be cardiac arrhythmia resulting from hypocalcemia associated with EDTA infusion and vasculature cardiomyopathy. The patient's ionized calcium level during code was 3.8 mg/dL (normal value for adult patients: 4.5--5.3 mg/dL) after one IV injection of calcium gluconate administered by emergency medical technicians en route to the hospital and another IV injection of calcium chloride in the ED. The Oregon State Naturopath Licensing Board is conducting an investigation to determine whether Na_2EDTA or CaEDTA was administered to this patient.

The cases described in this report have been reported to FDA. FDA is performing a safety assessment of Na_2EDTA , including a review of the adverse event reporting system to determine whether other deaths related to use of chelating agents have been reported.

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Editorial Note:

Both children and adults are subject to potentially lethal prescription errors involving "look-alike, sound-alike" substitutions (i.e., confusion of drugs with similar names). In a 1-year study of errors in a tertiary care teaching hospital, 11.4% of medication errors were found to have resulted from use of the wrong drug name, dosage form, or abbreviation (4). A review of medical records in the Texas case described in this report revealed that the brand names for the Na₂EDTA product, Endrate® (Hospira, Inc., Lake Forest, Illinois), and the CaEDTA product, Calcium Disodium Versenate® (3M Pharmaceuticals, St. Paul, Minnesota), were used interchangeably; this improper use of drug names likely resulted in the inappropriate administration of Na₂EDTA.

Although CaEDTA and succimer were ordered for one patient and the form of EDTA administered to another remains under investigation, these drugs singly or in combination probably were not responsible for the low calcium levels. Hypercalcemia as a result of IV administration of CaEDTA has been reported (5). Succimer by itself is a weak calcium binder but is not associated with a drop in essential minerals such as calcium (6). Moreover, the reported doses of CaEDTA and succimer in the Texas case were appropriate and within established safety limits.

Medical center records and coroner reports indicate that Na₂EDTA was administered in at least two of the cases. Na₂EDTA is often part of a standard hospital formulary; however, it should never be used for treating lead or other heavy metal poisoning in children because it induces hypocalcemia, which can lead to tetany and death (7). The error that caused the death in Texas most likely resulted from miscommunication between the pharmacy and the pediatric unit.

Chelation therapy with CaEDTA, dimercaperol, or succimer has been the mainstay of medical management for children with BLLs $\geq 45 \mu\text{g/dL}$ (1). The effectiveness of chelation therapy in improving renal or nervous system symptoms of chronic mercury toxicity has not been established. Nonetheless, certain health-care practitioners have used chelation therapy for autism in the belief that mercury or other heavy metals are producing the symptoms (8). Other practitioners have recommended chelation therapy for treatment of coronary artery disease, hoping to eliminate calcified atherosclerotic plaques that can lead to coronary artery occlusions and myocardial infarctions. These off-label uses of chelation therapy are not supported by accepted scientific evidence. The Institute of Medicine found no scientific evidence that chelation is an effective therapy for autism spectrum disorder (8). Because limited consistent data exist on the use of chelation therapy to treat coronary artery disease, a clinical trial to assess the safety and effectiveness of chelation therapy is being conducted by the National Institutes of Health.*

Deaths associated with lead poisoning are rare (9), and childhood deaths caused by cardiac arrest associated with chelation therapy have not been documented previously (9). As BLLs among children in the United States continue to decline (2), fewer children require chelation therapy. Primary care providers should consult experts in the chemotherapy of lead before using chelation drug therapy. If such an expert is not available, primary care providers should contact state or local childhood lead poisoning prevention programs or the Lead Poisoning Prevention Branch of the National Center for Environmental Health, CDC.

CDC and its state and local partners will continue to educate health-care providers and pharmacists to ensure that Na₂EDTA is never administered to children during chelation therapy. CDC recommends that hospital pharmacies evaluate the need to keep Na₂EDTA in their formularies. Case reports of cardiac arrest or symptoms of hypocalcemia during chelation therapy should be reported to the CDC Lead Poisoning Prevention Branch (770-488-3300) or to MedWatch, the FDA adverse event reporting system, at <http://www.fda.gov/medwatch>.

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* Additional information is available at <http://nccam.nih.gov/news/2002/chelation/pressrelease.htm>.

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