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Deaths Resulting From Hypocalcemia After Administration of Edetate Disodium: 2003-2005

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ABSTRACT

From 2003 to 2005, deaths of 3 individuals as a result of cardiac arrest caused by hypocalcemia during chelation therapy were reported to the Centers for Disease Control and Prevention. Two were children, both of whom were treated with edetate disodium. At the time of this writing, the adult case was still under investigation. No previous cases of death resulting from hypocalcemia during chelation have been reported. From our experience and review of the literature, we suggest that health care providers who are unfamiliar with chelation consult an expert before undertaking treatment and that hospital formularies evaluate whether stocking edetate disodium is necessary, given the risk for hypocalcemia and the availability of less toxic alternatives.

CHELATION THERAPY, USED in the treatment of lead poisoning, enhances urinary and/or biliary excretion of toxic and essential metals including lead, thus decreasing total body burden.¹ Over the past 30 years, environmental and dietary exposures to lead have greatly diminished, resulting in a dramatic decrease in population blood lead levels (BLLs) and a corresponding decrease in the number of patients requiring chelation therapy for lead poisoning.² Several chelating agents are available, including edetate disodium calcium (CaNa₂EDTA), the only intravenous (IV) chelating agent used in lead poisoning, dimercaprol (British anti-Lewisite), D-penicillamine, and *meso*-2,3-dimercaptosuccinate (succimer).³ Chelating agents, especially those intended for use in children, should be effective in reducing lead and other toxic metals from the body without producing significant adverse effects on levels of critical serum electrolytes such as calcium. Hospital formularies usually stock multiple chelation agents. One such agent, edetate disodium (Na₂EDTA), also administered IV, can be used for the emergency chelation of calcium, but its use has become infrequent because of concerns regarding nephrotoxicity and the availability of less toxic alternatives.⁴

Deaths associated with lead poisoning are rare, and childhood deaths caused by cardiac arrest associated with chelation therapy have not been documented previously.^{5,6} Here we report our experience with 3 deaths resulting from hypocalcemia during chelation therapy.

CASE REPORTS

In 2005, the Texas Department of State Health Services Childhood Lead Poisoning Prevention Program reported a case of chelation-associated hypocalcemia to the Centers for Disease Control and Prevention (CDC). The CDC made inquiries to state and local lead-surveillance programs for reports of chelation-related fatalities and subsequently identified additional cases in Pennsylvania and Oregon.

CASE 1. In February 2005, a 2-year-old girl tested for blood lead during routine health surveillance had a capillary BLL of 47 $\mu\text{g}/\text{dL}$. A venous BLL of 48 $\mu\text{g}/\text{dL}$ obtained 12 days later confirmed the elevated BLL. The child also was iron deficient. A complete blood count and iron study conducted concurrently revealed low serum iron levels and borderline anemia. On February 28, 2005, she

Key Words: hypocalcemia, lead poisoning, medication error

Abbreviations: BLL, blood lead level; Na₂EDTA, edetate disodium; CaNa₂EDTA, edetate disodium calcium; IV, intravenous(ly); CDC, Centers for Disease Control and Prevention; ED, emergency department

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was admitted to a local medical center for chelation therapy to reduce her BLL.

The patient's blood electrolyte levels at admission were within normal limits. Initial medication orders included IV Na₂EDTA and oral succimer. The medication order subsequently was corrected by the pediatric resident to IV CaNa₂EDTA. At 4:00 PM on the day of admission, the patient received 300 mg of CaNa₂EDTA in 100 mL of normal saline at 25 mL/hour IV. At 4:35 PM, she was administered 200 mg of oral succimer. Her vital signs remained normal throughout the night. At 4:00 AM the following morning, 300 mg of Na₂EDTA instead of IV CaNa₂EDTA was administered IV. One hour later, the patient's serum calcium had decreased to 5.2 mg/dL (reference value for pediatric patients: 8.5–10.5 mg/dL). At 7:05 AM, the child's mother noticed that she was limp and not breathing. Cardiac compression and O₂ via ambu bag did not restore a normal cardiac rhythm, and a cardiac resuscitation code was initiated at 7:25 AM. The child had no palpable pulse or audible heartbeat. Repeat laboratory values drawn at 7:55 AM showed that her 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 AM.

An autopsy revealed no results of toxicologic significance. A postmortem radiologic bone survey showed "lead lines," growth arrest and recovery in long bones as indicated by areas of sclerosis at the metaphyses. 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 indicate that a dose of IV Na₂EDTA was unintentionally administered to the child.

CASE2. In August 2005, a boy aged 5 years died while receiving 990 mg of Na₂EDTA IV pushed over 5 to 10 minutes in a physician's office. The child was receiving chelation as treatment for autism. The mother noted that the child was limp, and the physician initiated resuscitation. Emergency services were contacted to transport the child to the hospital. At the emergency department (ED), additional resuscitation efforts were attempted, including 320 mg of IV calcium chloride. 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 the 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 Na₂EDTA. This case is under investigation by the Pennsylvania State Board of Medicine.

CASE3. In August 2003, a 53-year-old woman with no evidence of coronary artery disease, intracranial disease, or injury was treated with 1500 mg of EDTA IV pushed over 10 to 15 minutes in a naturopathic practitioner's

clinic. The EDTA was intended to remove heavy metals from her body. The source and type of EDTA administered has not been determined. The practitioner had administered 5 previous chelation treatments consisting of both oral and IV agents to the patient over the preceding 2 months. Approximately 10 to 15 minutes after treatment began, the patient became unconscious. Cardiopulmonary resuscitation was initiated, and emergency services were contacted. Efforts 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 vacuolar cardiomyopathy. The patient's ionized calcium level during code was 3.8 mg/dL (reference value for adult patients: 4.5–5.3 mg/dL) after 1 IV injection of calcium gluconate by emergency medical technicians en route to the hospital and another IV injection of calcium chloride in the ED. This case was brought to the attention of the Oregon Board of Naturopathic Examiners by Oregon State Public Health.

DISCUSSION

Children are at high risk for medication errors in health care settings.⁷ Both children and adults are subject to lethal prescription errors involving "look-alike, sound-alike" substitutions. 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.⁸ A review of medical charts in the Texas case revealed that the brand names for the Na₂EDTA product, Endrate (Hospira, Inc, Lake Forest, IL), and the CaNa₂EDTA product, Calcium Disodium Versenate (3M Pharmaceuticals, St Paul, MN), were used interchangeably and likely resulted in the inappropriate administration of Na₂EDTA.

Although CaNa₂EDTA and succimer were ordered for 1 patient and the form of EDTA administered to another remains under investigation, CaNa₂EDTA and succimer singly or in combination probably were not responsible for the low calcium levels. CaNa₂EDTA is a nonspecific metal chelator that reduces zinc, lead magnesium, and copper levels.⁹ Hypercalcemia as a result of IV administration of CaNa₂EDTA has been reported.¹⁰ There are no reports of CaNa₂EDTA-induced hypocalcemia. Succimer by itself is a weak calcium binder but is not associated with a drop in essential minerals such as calcium.¹¹ Moreover, the reported doses of CaNa₂EDTA and succimer in the Texas case were appropriate and well within established safety limits.

Medical center records and coroner reports indicate that Na₂EDTA was administered in at least 2 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.¹² Furthermore, Na₂EDTA contains a boxed warn-

ing 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."¹³

Chelation therapy with CaNa₂EDTA, British anti-Lewisite, penicillamine, or succimer has been the mainstay of medical management for children with BLLs \geq 45 μ g/dL and for adults with symptomatic lead poisoning.¹⁴ The effectiveness of chelation therapy to improve renal or nervous system symptoms of chronic mercury toxicity has not been established. Nonetheless, some health care practitioners have used chelation therapy for treatment of autism in the belief that mercury or other heavy metals are producing the symptoms.¹⁵ 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.¹⁶ These off-label uses of chelation therapy are not supported by widely accepted scientific evidence. The Institute of Medicine found no scientific evidence that chelation is an effective therapy for autism spectrum disorder.⁸ Because little 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.⁹

CONCLUSIONS

Health care providers and pharmacists should ensure that Na₂EDTA is never administered to children during chelation therapy. The CDC recommends that hospital pharmacies evaluate the need to keep Na₂EDTA on 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 (www.fda.gov/med-watch), the Food and Drug Administration's adverse-event reporting system.

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